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# THE MECHANICAL FACTORS IN ARTERIOSCLEROSIS

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Few problems in medicine have received the attention accorded to that of arteriosclerosis. The index of a recent monograph (Cowdry) contains citations of eight hundred separate authors and some two thousand separate factual observations. And yet, current opinion as to the cause and the manner of development of the condition is exceedingly diverse and uncertain (MacCallum). Some of the commoner etiologic factors have been discussed under (1) toxins of infections—typhoid (Thayer and Brush), rheumatism (Klinge), arthritis (Nissen and Spencer); (2) chemical poisons, such as lead (Billings) and alcohol (Cabot); (3) dietary imbalance in salt (Thompson and McQuarrie), cholesterol (Leary), proteins (Nuzum and others), high fat diets (Warren); (4) endocrine disturbances—pituitarism (Moehlig and Osius), hyperthyroidism (Rolleston), diabetes (Joslin), disorders related to epinephrine (Josue); (5) vitamins (Kesten; Harrison); (6) vasomotor disturbances (Staemmler); (7) heredity (O'Hare and co-workers); (8) hypertension (Moschcowitz); (9) nephritis (Kimmelstiel and Wilson), and lastly (10) the strictly mechanical factors (Virchow; Allbutt).

Experimental sclerosis seems to have added little but confusion to the problem. It still leaves unsettled the four main questions: 1. Is fatty infiltration the cause of or is it incidental to sclerosis? 2. Are the initial changes in the intima (Leary) or in the media (Thoma)? 3. What are the mechanics of the initial thickening (Leary)? 4. Is hypertension the cause or the effect of sclerosis (Keith and Kernohan; Weiss and Ellis; Wiggers)?

In only one cardinal fact does there seem to be any agreement; that is, loss of elasticity is eventually a constant finding in sclerosis. This seems to be true for the aorta, the arteries and the arterioles. No vessels seem to be immune (Dow). The sclerosis may be nodular, diffuse, senile or simple and may occur at any age from birth to 90. Both the atheromatous and the Mönckeberg types (medial degenera-

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tion) increase with age (Sydenstricker). Patches may be multiple or single, and the heart alone may be attacked (Hollingsworth and McNamara).

It is of extreme interest to find in a review of the literature on arteriosclerosis that so few direct quantitative measurements have been made on elasticity. Since the work of Roy, only occasional attempts have been directed to determining the state of the arterial wall by other methods than simple palpation. Mayeda devised an elastometer and calculated Young's modulus for human arteries. Bramwell, Bazett and Dryer, Frank, Hemingway and his co-workers, and Hallock made indirect measurements by using the rates of conduction waves, which give the relative elasticity based on Moen's formula:

$$V = K\sqrt{g}\,\frac{E}{s}\,\frac{a}{d}$$

in which $V$ is the velocity of the pulse wave; $K$, a constant; $g$, the gravity; $E$, coefficient of elasticity; $a$, thickness of the arterial wall; $s$, specific gravity of the blood, and $d$, diameter of the vessel. Clark reviewed the subject in her work on the elasticity of veins and added a few measurements for arteries. Yater and Birkeland reverted to Roy's method, but they reported only on the relative elasticity with age. MacWilliams used the direct method, but Young's modulus is not calculated in his data.

I propose to approach the problem from several entirely new angles. Certain phases have been studied in tissues other than arteries. This categorical approach will be appreciated if it is recalled that the arterial wall is not homogeneous in its make-up but composed of muscle, elastic fibers and collagenous fibers, all of which presumably have different coefficients of elasticity.

## MATERIALS AND METHODS

With this point of departure, a series of elastrometric measurements were made on the ligamentum nuchae of the ox, a tissue in which smooth muscle plays no rôle. Here it is possible to determine Young's modulus for a given specimen and to determine the so-called aging factor, which is generally considered to exist and which is so cogent to Osler's aphorism that "man is only as old as his arteries." Any general etiologic factor affecting elasticity in the vascular bed must likewise have its effect on the elastic tissue at other sites if elasticity is a function of the elastic tissue.

*Elastometric Measurements on Ligamentum Nuchae of Ox.*—Fresh ligamentum nuchae was obtained from a local abattoir immediately after the animals were slaughtered. Strips of measured length were used; the volume was measured, the specific gravity determined, and the cross-sectional area calculated. Pieces were suspended vertically before a mirror bearing a millimeter rule. Two black threads were tied at convenient distances from the ends and their positions noted. Weights were applied; the positions of the threads were again noted and the stretch recorded. This method eliminates errors due to slip at the points of attachment. Readings were made at intervals of approximately fifteen seconds. Preparations were kept moist with Ringer's solution.

TABLE 1.—*Typical Test on Ligamentum from Yearling (Pierce 1e, Obtained March 11, 1936; Tested March 14, 1936*

Length of piece 1e, 6.09 cm.
Weight in air, 1.274 Gm.
Weight in Ringer's solution, 0.067 Gm.

Weight displaced in Ringer's solution...1.2070 Gm.
Specific gravity in Ringer's solution.....1.0093
Volume displaced in Ringer's solution...1.1959 cc.
Cross-section of piece V/L.....0.1890 sq. cm.

$$\text{Young's modulus} \frac{F \times L}{a \times dl}$$

Calculated for 1st 10 Gm.

$$\frac{10 \times 6.33}{0.189 \times 0.18} = 1.825 \times 10^6$$

| Weight Applied | Length, Cm. |
|---|---|
| String and hook..... | 6.09 |
| Pan 1 = 7.2 Gm. ..... | 6.33 |
| Gm. weights as follows: | |
| 5..... | 6.41 |
| 10..... | 6.51 |
| 20..... | 6.68 |
| 40..... | 6.92 |
| 50..... | 7.06 |
| 60..... | 7.10 |
| 80..... | 7.32 |
| 100..... | 7.51 |
| 120..... | 7.70 |
| 140..... | 7.98 |
| 190..... | 8.47 |
| 240..... | 8.97 |
| 340..... | 9.90 |

TABLE 2.—*Elasticity of Ligamentum Nuchae of Ox*

| Specimen | Age | Length, Cm. | Cross-Sectional Area, Sq. Cm. | Weight, Gm. | Modulus, Dynes per Sq. Cm. × $10^6$ |
|---|---|---|---|---|---|
| 1 c..... | Fetal | 9.580 | 0.4400 | 10.0 | 1.222 × $10^6$ |
| | | | | 20.0 | 1.042 |
| | | | | 50.0 | 1.570 |
| | | | | 100.0 | 2.340 |
| 2 c..... | | 5.540 | 0.1632 | 10.2 | 0.327 |
| | | | | 20.0 | 1.842 |
| | | | | 46.0 | 3.510 |
| 1 d..... | 6 weeks | 2.325 | 0.0785 | 12.2 | 5.040 × $10^6$ |
| | | | | 27.2 | 4.380 |
| | | | | 47.2 | 4.410 |
| | | | | 106.0 | 4.723 |
| 2 d (piece partly putrified*).... | | 2.100 | 1.4950 | 10.0 | 1.068 |
| | | | | 39.0 | 1.847 |
| | | | | 99.0 | 2.273 |
| 1 e..... | 1 year | 6.330 | 1.8000 | 10.0 | 1.825 × $10^6$ |
| | | | | 40.0 | 2.225 |
| | | | | 99.0 | 2.293 |
| 2 e..... | | 7.650 | 1.3120 | 10.0 | 1.465 |
| | | | | 40.0 | 2.216 |
| | | | | 99.0 | 2.850 |
| 1 h..... | 4 years | 9.760 | 1.4090 | 46.0 | 3.865 × $10^6$ |
| | | | | 105.0 | 4.458 |
| 2 h..... | | 9.260 | 1.2170 | 46.0 | 4.125 |
| | | | | 105.0 | 4.180 |
| 3 h (partly putrified*)..... | | 9.590 | 0.0905 | 46.0 | 4.340 |
| | | | | 95.0 | 2.850 |
| 1 g..... | 8 years | 9.100 | 2.2150 | 46.0 | 4.051 × $10^6$ |
| | | | | 105.0 | 5.142 |
| 2 g..... | | 10.270 | 2.3000 | 46.0 | 4.020 |
| | | | | 105.0 | 4.728 |
| 3 g (partly putrified*)..... | | 8.690 | 0.6780 | 46.0 | 4.711 |
| | | | | 105.0 | 3.110 |
| Average..... | | | | | 3.060 × $10^6$ |

* Kept in the icebox for from six to twelve days.

A typical test is detailed in table 1.

A portion of the data is presented in table 2. To include all of the measurements would have been entirely too cumbersome.

While there is considerable variation in the individual counts, they are all within reasonable limits with the one exception of 2c. The extremely low value may have been due to a technical error, since this tissue stretches considerably by its own weight. One interesting fact shown by the pieces kept until there was a detectable odor of putrefaction was a sharp decrease in the modulus at the higher weights. I question the significance of Roy's statement that putrefaction has no effect on elasticity.

A comparison may be made next between the values that may be calculated from Roy's data for the aorta and my data for ligamentum nuchae. Roy gave the data shown in table 3 on the stretch of pieces 1 cm. wide. If one takes the accepted thickness at 1.5 mm., Young's modulus may be calculated.

TABLE 3.—*Young's Modulus Calculated from Roy's Data on Elasticity of Aorta*

| Grams | Transipiece, Mm. | Modulus Calculated from Roy's Data, Dynes per Sq. Cm. × $10^6$ | Longipiece for Comparison, Mm. |
|---|---|---|---|
| 0 | 18.0 | ..... | 18.0 |
| 50 | 23.8 | $1.015 \times 10^6$ | 25.5 |
| 100 | 27.0 | 1.306 | 26.7 |
| 150 | 27.9 | 1.784 | 27.2 |
| 200 | 28.4 | 2.342 | 27.4 |

TABLE 4.—*Comparison of Present Data with Results Obtained by Mayeda's Method*

| Age, Years | Modulus Calculated from Mayeda's Results, Dynes per Sq. Cm. × $10^6$ | Modulus Calculated from Data on Ligamentum Nuchae, Average |
|---|---|---|
| 3 | $0.21062 \times 10^6$ | $3.060 \times 10^6$ |
| 9 | 0.23443 | |
| 20 | 0.24175 | |
| 28 | 0.23864 | |
| 37 | 0.23521 | |
| 49 | 0.23506 | |
| 55 | 0.26874 | |
| 60 | 0.33329 | |
| 65 | 0.34317 | |
| 72 | 0.34441 | |

Next a comparison may be made with the results obtained by Mayeda's percussion method, designed to eliminate Weber's after-action. The effect of aging in the aorta is shown in his figures, which are given in table 4.

It is worthy of note that Mayeda shows a lower modulus for longitudinal strips of the aorta than for transverse. The average is $0.18106 \times 10^6$. This is not in keeping with the general observations of Roy.

One of the most interesting results obtained from these comparisons is that the modulus for strips of the aorta is very much less ($0.23846 \times 10^6$) than that for elastic tissue of the ligamentum nuchae ($3.060 \times 10^6$). This may be taken to mean that elasticity is not a function of the elastic tissue per se but rather a function of the architectural arrangement of the fibers. This fact should have been self-evident, but I was not aware of it until the calculations made it apparent. By way of an analogy, no man will select a bed of iron with an elasticity coefficient of 19,700, but he will utilize this material in the construction of flat bed-springs and be quite comfortable.

This relationship is further shown by a comparison of the measurements made by Clark for arteries, which were calculated on the degree of distention at various pressures and converted into Young's modulus (table 5). The age and the specific vessels are not cited. Her data bear out the statement of previous observers that Young's modulus is not a constant at all pressures. She indicated one significant criticism of both Roy's and Bramwell's method in that neither considered the thickness of the wall of the vessel with which he was dealing. Loss in elasticity with age may be entirely due to the variability in the relation between the radius and the thickness of the wall (r/t), and hence the matter becomes a simple mechanical problem rather than a loss in elasticity per se.

The relative elasticity of blood vessels has been worked out by methods making use of the pulse wave. Allbutt seems to have used this technic before Bramwell, since he cited the data given in table 6.

TABLE 5.—*Comparison of Clark's Data on Arteries with Present Data*

| Pressure, Cm. Hg | Elasticity | Modulus Calculated from Clark's Data, Dynes per Sq. Cm. × $10^6$ | Modulus Calculated from Present Data, Dynes per Sq. Cm. × $10^6$ |
|---|---|---|---|
| 1-2 | 121 × $10^6$ | 1.45 × $10^6$ | 3.060 × $10^6$ |
| 2-3 | 141 | 1.68 | |
| 3-4 | 144 | 1.68 | |

TABLE 6.—*Allbutt's and Bramwell's Data on Relative Elasticity of Blood Vessels*

| Allbutt | | Bramwell | |
|---|---|---|---|
| Age, Years | Wave Velocity, Mm. per Second | Age, Years | Relative Elasticity |
| 4½ | 216 | 5 | 0.47 |
| 25 | 306 | 30 | 0.28 |
| 40 | 416 | 40 | 0.24 |
| 50 | 510 | 50 | 0.22 |
| | | 80 | 0.17 |

Wiggers gave a critical analysis of the technical difficulties involved in this method and reviewed the data of Frank. All tests bear out the contention that there is a loss in distensibility with age, but the methods are so variable that no direct comparisons are possible. The more direct measurements of MacWilliams indicate the same general phenomenon, but his apparatus was not calibrated, and hence Young's modulus is not directly calculable. His curves differ for contracted and relaxed vessels.

I next present, in table 7, the data on elasticity in ligamentum nuchae as affected by increasing age. From this table there seems to be no relative loss in elasticity in ligamentum nuchae with increasing age.

If one examines some of Roy's figures carefully, the same phenomenon is seen in the aorta except in extreme age (table 8).

The same relationship was demonstrated by Yater and Birkeland, who found increase in elasticity from childhood to the twenty-seventh year and sharp reduction thereafter.

*Comparison of Modulus of Ligamentum Nuchae with That of Other Tissues.*—In view of the fact that the blood vessel contains smooth muscle, I had hopes of analyzing the separate rôles of the elastic tissue and muscle in the elasticity of

the aorta. The work of Haycraft on smooth muscle was disappointing in this respect, since Young's modulus was not calculated, nor was the apparatus calibrated, nor were the sizes of the pieces given. The only point of interest shown by his data is that muscle is not completely elastic when subjected to great stress. This may indicate a cause for MacWilliams' sigmoid curves for the distention of contracted vessels and support the contention that muscle imparts tone to the wall of a vessel. This point is indirectly confirmed by the decrease in Young's modulus after death (Mayeda).

For the sake of comparison, it is of some interest to introduce the data for the relative elasticity of other tissues. Fick gave the following figures: collagenous tissue, from 25 to 100; elastic tissue, from 0.02 to 0.01. Landois gave the values: tendon, 1.6693; passive striate muscle, 0.2734; coats of the artery, 0.0726. These values are not expressed in Young's modulus.

TABLE 7.—*Data on Elasticity in Ligamentum Nuchae as Affected by Age*

| Age | Length, Cm. | Cross-Sectional Area, Sq. Cm. | Weight, Gm. | Young's Modulus,* Dynes per Sq. Cm. × $10^6$ |
|---|---|---|---|---|
| Fetal | 9.58 | 0.0652 | 46.0 | 3.510 × $10^6$ |
| 6 weeks | 2.82 | 0.0785 | 47.2 | 4.410 |
| 1 year | 6.33 | 1.8900 | 40.0 | 2.225 |
| 4 years | 9.76 | 1.4030 | 46.0 | 3.856 |
| 8 years | 9.10 | 2.2150 | 46.0 | 4.051 |

* Young nodulus for ligamentum nuchae was taken for about the same weight, i. e., 45 Gm.

TABLE 8.—*Roy's Relative Stretch of Aorta for Age*

| Age, Years | Length of Piece, Mm. | Length with Given Weight Attached, Cm. | | |
|---|---|---|---|---|
| | | 50 Gm. | 100 Gm. | 200 Gm. |
| 2½ | 100 | 131 | 148 | 159 |
| 9 | 100 | 128 | 140 | 160 |
| 26 | 100 | 128 | 149 | 168 |
| 71 | 100 | 113 | 117 | 121 |

## HISTOPHYSICAL OBSERVATIONS

From the foregoing studies no definite conclusions may be drawn as to the relative elasticity value of any one histologic element in the arterial wall; hence the relation of muscle atrophy or elastic degeneration, so called, to loss in elasticity with aging must be purely speculative. I believe that loss in elasticity with age is due to fibrosis—not to a replacement of muscle or elastic tissue per se but to a deposition which interferes with the netlike arrangement of the fibers. The mechanism responsible for this will be outlined subsequently.

A very interesting consideration arises from a review of these conditions. It is generally believed that fibrosis is a compensatory process for strengthening a wall that has become weak and distended with age. I believe that *the thinning of the wall and the distention of the aorta*

*are a compensatory process tending to reestablish the elasticity of youth,* following an initial fibrosis due to irritational hyperplasia. As indicated by Clark, loss in elasticity may present a simple mechanical problem, in which the ratio between the thickness of the vessel wall and the diameter of the lumen becomes abnormal. Thickening in the intima progresses more rapidly with age than thickening in the media. It begins very early in life. Hence it is highly improbable that the fibrosis follows angiomalacia. Fibrosis alternating with compensatory thinning may be pictured as a universal process extending throughout life.

This relationship is supported by the calculations in table 9. The figures for the circumference of the aorta with age are from Kaufman and Aschoff, those for the thickness of the wall are from Schäfer and those for the relative elasticity are from Bramwell. I offer the following formula as a new point of departure in subsequent studies that deal with the histophysics of the aorta.

$$C \times T \times E = K$$

TABLE 9.—*Changes in Measurements and in Elasticity of Aorta with Age*

| Age, Years | Circumference of Aorta, Mm. | Thickness of Wall, Mm. | Relative Elasticity | K (Product) |
|---|---|---|---|---|
| 20 | 57.4 | 0.910 | 0.33 | 17,237 |
| 30 | 61.0 | 1.120 | 0.28 | 19,129 |
| 50 | 70.0 | 1.256 | 0.22 | 19,342 |

in which $C$ is the circumference, $T$ the thickness of the wall and $E$ the relative elasticity. $K$ is a constant. A similar hypothesis has been independently developed by Bazett, Cotton, Laplace and Scott.

In concluding this section I wish to point out the following significant facts:

1. There is no decrease in the elasticity of elastic tissue per se with age.

2. Marked discrepancies are present in the values of Young's modulus for the elastic tissue per se.

3. The curves for the elasticity of the aorta have not been analyzed into the rôles played by muscle, elastic tissue and collagenous tissues.

4. A new interpretation may be put on distention and thinning of the aorta. These alterations may represent a factor other than that of functional degeneration.

The measurements of the elasticity and the calculation of Young's moduli of the ligamentum nuchae of the ox were made by Elkin Vogt of the department of physiology of the University of Georgia School of Medicine.

### HISTOLOGIC OBSERVATIONS

Counts have been made of the relative numbers of blood vessels per given cross-sectional area of the ligamentum nuchae at different ages, since certain theories of arteriosclerosis are based on the concept of interference with the blood supply. The data are presented in table 10. It is significant that there is a general reduction in the vascularity of the tissue with age.

Attention is also called to the relative loss in the number of cells, generally indicative of senescent changes in a tissue, but here neither the number of cells nor the vascularity seems to have affected elasticity, since the sections were cut from pieces tested as stated in the first half of this paper.

TABLE 10.—*Number of Blood Vessels per Square Millimeter of Ligamentum Nuchae at Different Ages*

| Age of Animal | Vessels per Sq. Mm. | Nuclei per Sq. Mm. |
|---|---|---|
| Fetus | 128.0 | 16,000 |
| 6 weeks | 14.0 | 3,200 |
| 1 year | 6.0 | 2,000 |
| 8 years | 4.0 | 800 |
| 15 years | 2.6 | 400 |

TABLE 11.—*Size of Elastic Fibers of Ligamentum Nuchae at Different Ages*

| Age of Animal | Size of Fibers, Planimeter Units | Standard Deviation | Size of Fibers, Sq. Microns |
|---|---|---|---|
| Fetus | Fibrillar | | |
| 6 weeks | 5.4483 ± 0.1773 | 2.001 | 23.070 |
| 1 year | 7.0612 ± 0.3218 | 3.340 | 30.000 |
| 8 years | 7.7347 ± 0.0290 | 3.013 | 32.525 |
| 15 years | 12.7545 ± 0.0946 | 1.480 | 53.070 |

Again, measurements have been made (table 11) of the size of the elastic fibers at various ages, which is significant since so-called fiber splitting and delamination are considered a conspicuous and important feature of early sclerosis. The method was to draw the fibers with the camera lucida, measure the areas with a Koessel planimeter, calibrate and reduce to square microns.

It is evident in table 11 that there is a progressive increase in the size of the fibers with age; hence fiber splitting is not a senescent factor in elastic tissue per se, and some other factor must be sought in arteriosclerosis. I should suspect this on embryologic grounds since Jackson has shown delamination in the 120 mm. human embryo.

As a final observation concerned with aging, I may state that tests for fatty infiltration in the fibers of the 15 year old animal failed to give positive results. There was also no evidence of granular disruption

of the fibers. This is of interest since fragmentation is a common observation in sclerosis. It may, however, be incidental to the interference of a blood supply, since Harvey found fragmentation within thirty-three days after transplanting one blood vessel to a subcutaneous position in another, and within ten days if the vessel was stretched.

In concluding the section, I may point out that all of the measurements are simple, direct and unequivocal. In themselves they do not constitute a solution of the problem of arteriosclerosis, but they indicate certain probabilities which make certain theories acceptable and others untenable. The data question: (1) the loss of elasticity with age of elastic tissue per se; (2) the effect of vascular supply on the tissue per se; (3) fiber splitting as a senescent process; (4) the direct action of any metabolite or poison on elastic tissue per se. Hence I extend this search for a primary etiologic factor in arteriosclerosis into the strictly mechanical processes that affect the micro-architecture of the vessel wall.

## INTIMAL HERNIATION: A MECHANICAL THEORY OF THE ETIOLOGY OF ARTERIOSCLEROSIS

Before presenting the detailed morphologic and physical principles on which my opinion is based I shall review the various mechanical theories previously advanced.

*Allbutt's Hypothesis ("Shearing").*—Allbutt, in search of a *novum primum* of intimal thickening, premised a shearing or a slip between the intima and the media, with a hypertrophy to stress, as in a "tree to the leeward." If, however, one makes calculations as to the amount of slip with distention and relaxation of the aorta, it is seen that this factor is negligible. When one applies Clark's formula for the thickness of the wall relative to the radius of a vessel ($2\ r/t = 13$) the thickness becomes 7.5 per cent of the diameter. For purposes of further discussion this may be distributed to the three coats as follows: intima, 0.5 per cent; media, 6 per cent; adventitia, 1 per cent. (These values approximate the relative thicknesses figured by Bremer.) Next the relative stretch may be calculated when the diameter of the lumen is doubled:

| | Relative Diameter | Intimal Circumference | Intimal Circumference with Lumen Doubled | Relative Stretch |
|---|---|---|---|---|
| Lumen | 100 | 3.1416 | 6.2832 | 2.000 |
| Lumen + intima | 101 | 3.1730 | 6.3146 | 1.990 |
| Lumen + media | 112 | 3.4186 | 6.6602 | 1.948 |
| Lumen + adventitia | 115 | 3.6128 | 6.7544 | 1.872 |

Thus when the diameter of the lumen is doubled the circumference of the intima doubles, but the inner wall of the media at the same time increases to only 199 per cent. This gives a shearing factor of only 1 part in 200 or 0.5 per cent. Meanwhile the adventitia stretches only 187 per cent, with a shearing factor of 7.6 parts in 194 or 3.8 per cent. Thus the shearing between the adventitia and the media is the greater, and this observation seems to support the opinion of Shennan and Pirie that tube wear comes between the middle and the outer third of a cylinder, producing faults, as engineers maintain.

Shearing would vary with the degree of distention, but doubling the diameter seems to be the practical limit of distention, as judged by the data of MacWilliams and Mackie on distention of the brachial arteries after death.

Shearing with the normal diastolic-systolic cycle is practically negligible. With the volume of the aorta varying from 255 to 190 cc., the wall stretch is approximately 15 per cent (and the shearing is $0.005 \times 0.15 = 0.00075$).

If this method is applied to the data of Roy on the increase in volume with varying pressures (normal, 126/64; hypertension, 204/115) the results are of interest. The data given by Roy are as follows: At 60 mm. of mercury the relative volume was 7.2; at 130 mm., 12.1; at 120 mm., 11.8; at 200 mm., 12.6. Neglecting increase in length, one finds that when the area is 7.2 the relative circumference is 2.99; when 12.1, 3.79; when 11.8, 3.75, and when 12.6, 3.92. Or, the stretch due to pressures from 60 to 130 mm. is 26 per cent; from 120 to 200, 4.5 per cent. This, of course, is for the whole wall. Hence the shearing factor of 0.5 per cent is again practically nil in both the normal and the hypertensive states.

Further proof that the shearing factor is practically nil in the data of Roy is found in the fact that the elasticity of the aorta is little affected when the intima or the adventitia is removed. Allbutt admitted that it is probably on the elastic fibers of the intima that lateral stress first begins to tell injuriously.

*Virchow-Aschoff Theory ("Loosening" and "Imbibition").*—Aschoff made "loosening of the connective tissue ground substance" his initial premise. He elaborated this further by assuming that swelling occurred due to increased imbibition, as evidenced by the width and the homogeneity of the connective tissue spaces. Connective tissue produces local thickenings, and fatty infiltration follows.

He did not account for the initial loosening, except for the observation that it may occur at points of fixation such as the points of origin of the intercostal arteries: "Where the vessel wall is under greatest tension, there must occur a more marked molecular wear and tear."

This hypothesis fails to account for the general distribution of sclerotic lesions, as in the trabecular arteries of the spleen or atheromas on the lappets of the mitral valves (Sato).

*Adami's Theory ("Strain").*—Adami's main tenet is that a weakening of the media is fundamental, which is followed by a strain, inducing the hypertrophy that is responsible for the new layers of the intima. This hypothesis is difficult to prove or to disprove, but many observations indicate that the initial stages may appear in specific cases before any lesions in the media are evident.

*Duguid's Hypothesis ("Fixation").*—After a consideration of the dynamics of the three coats and the lengthening of the aorta with every systole, Duguid expressed the belief that fixations such as those at the origin of the intercostal arteries have a tendency to act as "drags," producing "splits and chinks" and separating the intima from the media, with subsequent thickenings and bulgings. This leads to impairment of the relative elasticity of the intima through proliferation of the connective tissue and fatty infiltration. The amount of damage depends on the extent of excursion through which the tissue passes by reason either of hyperpiesia or of local fixation. Even in the toxic states, he thought that pulse pressure may be the factor responsible for the lesion. Moschcowitz adopted this hypothesis in part, but it will hardly explain his most valuable observation on the distention and fibrosis of the minor vessels in the lungs. Moschcowitz admitted, however, that neither hypertension nor fixation will account for "the vagaries of either regional or localized distribution of sclerosis."

*Harrison's Theory ("Mechanical Strain").*—Harrison by adopting the technic used in the production of atheroma by feeding (1) cholesterol and (2) vitamin D was enabled to demonstrate for the first time a mechanical factor. He found that the secondary lesion produced by one agent is not superimposed on the lesion produced by the first but comes at a point of mechanical impairment. He concluded that movement of parts is essential to the production of atheroma. I have no criticism of this hypothesis to offer other than that it fails to account for the primary lesion.

*Leary's Theory ("Stress and Stomata").*—Leary, who considered arteriosclerosis to be a nutritional disease, recognized a mechanical factor that interferes with local nutrition, and he adapted Lange's view of endothelial stomas to account for the diffusion of fats from the blood stream.

The question of the "stomata" has already been a "fighting phase" with histologists. I have never seen them except in the mesothelium of the diaphragm (Allen). Nothing comparable is seen in the vascular endothelium.

In concluding this critique I may say that all of the aforementioned hypotheses represent attempts to visualize the mechanics of the production of the initial lesion. They are all based on acceptable postulates, but they all fail to take into account the fundamental character of the vessel wall. In this respect I believe that I am warranted in adding one more opinion to the vast literature on the etiology of arteriosclerosis and I propose a theory of intimal herniation.

Any theory of sclerosis must be universal, applicable throughout all periods of life and to all grades of vascular structure. Hence there is little wonder that no agreement has been reached on a mechanical theory of the etiology since so much confusion exists as to the normal structure of the vascular wall. The aorta alone presents so variable a picture in the various textbooks that it would scarcely be recognized by rival histologists. Few authors have dealt with the aorta as distinct from the arteries (Krafka).

It might prove profitable to review some of the more general accounts. Maximow and Bloom described the intima as having a thickness of 127 microns. The subendothelial layer consists of a thin homogeneous or striated interstitial substance. A small number of long thin interlacing fibers support the stellate fibroblasts. The internal layers are striate because of a splitting of the internal elastic membrane. Some authors have described an intermediate layer of a homogeneous or striated interstitial substance that stains like mucoid.

Cowdry listed the following layers: first the endothelium, then a feltwork of subendothelial elastic fibers, backed by a longitudinal striate layer and a fenestrated membrane. This grades into the media.

Aschoff spoke of an endothelium, a subendothelium, elastic fibers of the intima, an elastic stria terminalis, an outer longitudinal elasticomuscular layer and an internal elastic membrane. He referred constantly to a "cement substance" and a "mucoid ground substance."

I have verified the occurrence of the fenestrated membrane and the striated longitudinal layer by examining teased preparations of a human aorta boiled in water for one hour. Acetic acid dissociation and pepsin digestion were not so successful.

Huber questioned the use of the term "fenestrated membrane." He substituted the idea of a fine feltwork of larger fibers paralleling the long axis of the vessel. Dees reviewed the technical approach to the demonstration of the fenestrated membrane and redescribed it in the terms of Henle and Ranvier. Her illustrations show the fenestrae to be from 9 to 13 microns wide; the lamellae are described as 2.5 microns thick. My own measurements for the fenestrae vary from 5 to 30 microns. More fenestrae have been seen at the points of exit of the arterial branches, and one characteristic is that the fenestrae are "nested."

Schaffer speaks of a *netzförmige, gefensterte und durchlöcherte elastische Fasernetze* (retiform, fenestrated and riddled elastic fiber network). Measurements made on the fenestrae as shown in his illustrations make them about 32 microns long. E. A. Schäfer followed Grundstein's description (widely copied) and stated that where the iliac arteries pass over into the aorta an internal elastic membrane is no longer recognizable. He stated further that every transition is met with between a longitudinal network and a fenestrated membrane.

Another point of confusion is the number and origin of the elastic laminae and how many to incorporate in the intima. In the aorta, the total number is generally given as from 40 to 85; the thickness as from 3 to 5 microns, and the interspaces as from 6 to 18 microns. Thayer and Fabyan showed the so-called splitting in the internal elastic membrane in the radial arteries, beginning with the seventh month. Some attempts have been made to consider the duplication of laminae as due to incorporation of new elastic fibers from the endothelium. This is based on Schaeffer's study of the closure of the ductus venosus, from nine to fourteen days after birth. Here the increase would occur as a compensatory process effecting a closure of the channel under reduced vascular pressure—a point in favor of Thoma's theory of sclerosis. A critical review of Schaeffer's work fails to establish his conclusion as to the origin of these fibers.

Jackson's studies on the histogenesis of the aorta show "splitting" of the internal elastic membrane at the 120 mm. stage for man. Furthermore, Tuthill showed three types of localized "splitting, knotting and fraying" in the cerebral arteries at 8 months, which cannot be explained on the basis of new fiber formation in the intima.

Thickening of the intima in localized patches was shown by Torres to occur at 6 weeks and was presented under his discussion of pachymenia in relation to juvenile sclerosis. He expressed the belief that

the aorta grows in patches and accounted for the spotty character on the basis of the distribution of the vasa vasorum as worked out by Robertson for the aorta. The observations are of extreme interest, but the explanation is doubtful since there is an open question as to whether or not the vasa reach the intima even in the juvenile period.

The generalized thickening of the intima with age as compared with the increase in the media presents still another problem. The values which Schäfer gave for the relative age changes in the thickness of the three coats are presented in table 12. This thickening cannot be entirely a question of the volume of blood flow, since immediately before birth the vascular bed is 50 per cent larger than after birth (Krafka). Thickening is a continuous chronological process the causative factor of which in the intima is different from that in the media.

With this review I may pass next to the factors which in my opinion are responsible for the thickening of the intima—localized in infants, diffused in the aged.

TABLE 12.—*Schäfer's Measurements of Thickness of Arterial Coats at Different Ages*

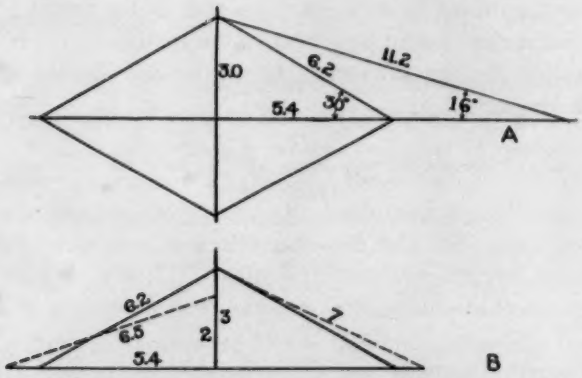
| Age | Intima, Microns | Media, Microns | I/M | Adventita, Microns |
|---|---|---|---|---|
| Birth | 6 | 650 | 1.0 | 1,485 |
| 16 years | 54 | 856 | 6.3 | 688 |
| 35 years | 124 | 996 | 12.4 | |
| 50 years | 181 | 1,075 | 16.8 | |
| 70 years | 190 | 1,111 | 17.1 | |

One of the established facts of hydrodynamics is that the greatest distortion is produced on the inner wall of the vessel; in this instance, the intima. The pressure of systole is transmitted through the endothelium and the subendothelium to the internal elastic membrane and the media. I believe that this force is not concerned primarily with a distention of the elastic tissue per se but rather with a widening of the interspaces in the network of muscle and elastic fibers. This force is demonstrable, as shown by Kokott, in its influence on the angulation of the fibers of the net. His calculated angulation of 35 degrees is supported by a measured angulation of 30 degrees for the inner coats and a greater and greater angulation up to 50 degrees under the adventitia.[1]

1. Both Kokott and Benninghoff spoke of the aortic wall as built of a series of concentric lamellae with reciprocal angulation in the successive layers, similar to the so-called osteon of the haversian systems in bone. While this concept is valuable, it is not strictly correct, since either a longitudinal or a transverse increase would have a rotary effect on the spiral which would play havoc with the insertions of the branch arteries. This rotary effect can be easily demonstrated by drawing out a spirally rolled tube of paper.

While the fibers per se are distributed in a spiral fashion, as has been demonstrated with preparations dissociated by means of acetic acid, they are so bound together as to produce a network which gives in the longitudinal as well as in the circumferential direction. Tigerstedt stated that the longitension in the dog's aorta is equal to about 50 to 90 mm. of mercury, i. e., below the mean blood pressure. It is a common observation that a part of the systolic pressure is expended against this longitension.

Calculations made on the diamond-shaped interspaces by using the angulation of Kokott present some interesting conclusions that support my hypothesis that the pattern of the net provides the essential elasticity.




*A*, diagram to illustrate the effect of distention of the arterial lumen on the fiber in the internal elastic membrane. *B*, diagram to illustrate the effect of the normal range of an arterial diastole-systole on the fiber in the internal elastic membrane.

If the triangle (one fourth of the diamond *A* in the accompanying figure) is constructed on the basis of altitude 3, base 5.4 and hypotenuse 6.2 with an angle of 30 degrees, when the base is doubled the angle becomes 16 degrees and the hypotenuse 11.2. Hence a doubling has been secured in the transidiameter by stretching the fiber (hypotenuse) only 1.8 times or 10 per cent less than if the fibers were strictly circumferential.

Again if the base is increased only 15 per cent (normal range for a diastole-systole) the fiber (hypotenuse) stretches only 12.9 per cent (*B* in the figure).

Or, if the longiaxis is reduced from 3 to 2 a 15 per cent increase in the transiaxis is secured with only a 4.6 per cent stretch in the fiber.

While this is only a hypothetic analysis of the interplay of the fibers, Rendez has demonstrated distortion of the interspaces by use of his micromanipulator.

That the pressure is exerted agaist the stress of distortion of the netlike structure is shown by the fact that the modulus of aortic strips approaches that of ligamentum nuchae only when the limits of elasticity are reached (Roy: 200 mm. Modulus is $2.342 \times 10^6$; ligamentum nuchae, $3.060 \times 10^6$).

Attention may now be directed to the interstices between the fibers and the problem of intimal herniation. The interstices between the fibers and the fenestrae in the solid membrane are points of tensile weakness. Under pressure, they can lead only to a microscopic degree of herniation. This must inevitably lead to irritational hyperplasia such as has been widely demonstrated in other tissues. Local points of either pathologic or physiologic weakness which emphasize this structural feature and widen the interspaces will produce local thickenings. Hence the end-results will be the same whether the process starts in inflammation of the vasa vasorum as in rheumatism, in necrosis of the muscle fibers as in epinephrine-induced sclerosis or directly in the intima itself, in edema (Klotz).

This point of view is supported histologically (1) by fiber splitting through increase in collagenous tissue to produce "splits and chinks" (Duguid); (2) by Benninghoff's demonstration of the fibrillar attachment of muscle in the subendothelial layer through fenestrae in the internal elastic membrane; (3) by endothelial indentations in the thickened intima (Perla and Deutsch).

I have found repeated evidences for such a concept in: (1) the nature of the crinkling of the internal elastic membrane in arteries, which is deep, regular and spaced—widely different from the uneven folds that form the wall of the stellate lumen of the umbilical artery, due to haphazard contraction; (2) tension lines of fibers and nuclei in oblique cuts of the fetal aorta, suggestive of fibrous septums, although not as definitely organized as retinacula.

Analogous buckling, binding, fraying, enlarged interstices and areas of local weakness may be seen in an old worn-out garter. The interplay of the various fibers in the network may be readily seen in stretching and relaxing such a model.

These weak spots are readily demonstrable in sections of the human aorta if the plane of section is taken tangential to the intimal surface. The size of the interstices and their arrangement are variable (from 3 to 30 microns), and the nuclei seem to ride the sides of the fibers, where they must be subject to considerable compression, extension and distortion. They occur in the first sections of the intima and extend throughout the media.

These weak spots are significant if it is borne in mind that they expand and contract with every heart beat and are further subject to

modification by the compensatory adjustments of the *spann* (tensor) muscles in regulating the "tone" of the vessel in temporary physiologic states and permanent pathologic conditions.

If there still exists a doubt as to the effects that the hydrostatic pressure is capable of producing, a review of the histology of the arteries during the period of establishment of collateral circulation is convincing. Sčelkunow ligated the aorta and recorded the following changes in the collateral circulation: (1) first a rupture of the layers of the wall; (2) an intense development of the connective tissue, rich in elastic fibers, most marked in the intima. Changes began within five days, reached a climax in three months and ended in a picture of a typical artery in five months.

In conclusion I may say that (1) interstices exist; (2) a variable pressure is always present; (3) herniation is inevitable. This provides a simple mechanism for the so-called irritational hyperplasia.

With this simple mechanical scheme, continued hyperpiesis is not absolutely necessary but may be a contributing factor to sclerosis. A temporary heightening of the pulse pressure may be effective. Sclerosis in the lesser circulation under a low blood pressure is to be expected if a relative increase is maintained, as in mitral stenosis or cardiac anomalies. Furthermore, the same factor is at play in the capillaries of the kidneys with irritational hyperplasia following herniation through the basement membrane as in the intracapillary sclerosis in nephritis described by Kimmelstiel and Wilson. The same effect is seen in the capillaries of the lungs as described by Moschcowitz.

The occurrence of sclerosis in the nonbranching portions of vessels, particularly those subject to longidistention (as the ascending aorta), becomes rational. "Branch tug" and fixation points such as may be observed in the carotid canal emphasize the size and character of the interstices and hence become common sites.

Splitting of the laminae (regular and irregular), "fraying" and localized "patches" offer no difficulties. The increased frequency of sclerosis with puberty may be explained on the ground of a rapid, uneven growth which brings out the structural defects which produce the initial intimal thickening. I do not propose to deal with the subsequent changes in sclerosis. Many investigations indicate the course. Newly injured tissue is subject to fatty infiltration, cholesterol deposition and calcification (Duff). Mucoid and "cement substance" changes have been fully dealt with by Schultze in an exhaustive study with a bibliography of eight-six titles.

SUMMARY

Direct measurements have been made on the elasticity of ligamentum nuchae and the coefficient expressed as Young's modulus (average,

$3.060 \times 10^6$). There is no consistent change in this modulus with age. The modulus is ten times that given for the aorta ($0.21062 \times 10,^6$ by Mayeda). This discrepancy is interpreted as due to the netlike arrangement of the elastic "skeleton" in the aorta and arteries.

The fiber size, relative vascularity and relative cellularity of the ligamentum nuchae have been determined for various ages. The results question many current theories of the etiology of arteriosclerosis and support the opinion of a primary mechanical factor.

A new theory of intimal herniation and irritational hyperplasia is advanced on histophysical grounds. It has the advantage of previous theories in that it is based on a universal principle of the interplay of elastic, muscular and collagenous tissue; it is not limited to any one age period nor to any special locality; it incorporates the "branch tug" hypothesis and is rational under any condition acting as direct causative agent, such as infection in the vasa vasorum, medial degeneration or intimal edema. It accounts for the frequency of sclerosis in hypertension but does not exclude the occurrence of sclerosis under the conditions of low pressure in the lesser circulation. It is consistent under the various physical conditions existing in the radicals of the vascular bed, including the aorta, arteries, arterioles and capillaries.

An incidental teleologic finding is that the relative dilatation of the aorta with age is not due to senescent weakening but is a compensatory process which attempts the reestablishment of the initial elasticity by altering the ratio between the thickness of the wall and the diameter of the lumen.

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# EFFECT OF ACUTE SCURVY ON THE GUINEA-PIG HEART

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Rinehart and Mettier [1] and Rinehart, Connor and Mettier [2] reported that guinea-pigs in a condition of scurvy with a concurrent streptococcic infection exhibit degenerative and proliferative lesions on the heart valves and in the synovial and periarticular tissues of various joints. They compared these lesions to those of rheumatic fever and hypothesized that the latter disease may be a response of scorbutic tissue to streptococcic infection. Schultz [3] corroborated their results in part.

In these results several points may be mentioned which make it appear that the lesions may be the effect of scurvy on the heart. First, so far as can be determined from the reports, the pathologic changes apparently occurred with equal frequency in both the animals that had acute and those that had chronic or subacute scurvy with superimposed infection. Second, according to the protocols given, the animals which were on a diet productive of a chronic or a subacute scorbutic condition and which had a superimposed streptococcic infection exhibited at autopsy some of the gross findings of acute scurvy. The same type of lesions, but of lesser degree, were described as observed in the animals with acute and chronic scorbutic conditions without infection.

Since it is improbable that clinical acute rheumatic fever is a condition of acute scurvy, it is considered desirable to determine whether

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From the House of the Good Samaritan.

The expenses of this study have been defrayed by a grant from the Commonwealth Fund.

1. Rinehart, J. F., and Mettier, S. R.: Am. J. Path. **10**:61, 1934.

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or not the lesions described are the result of acute scurvy in the guinea-pig heart. In view of the work of Wolbach and Howe [4] on the nature of pathologic conditions due to a deficiency of vitamin C, it may be expected that lesions similar to those described might occur in areas of severe stress or injury to the interstitial connective tissue structure. These lesions are not considered by us to be identical with, or even closely related to, those of acute rheumatic fever in human beings.

It is our purpose in this paper to give the results of a study of the effect of scurvy on the guinea-pig heart both in the absence and in the presence of concurrent streptococcic infection.

## METHOD

*Diet.*—The scurvy-inducing diet of Wolbach and Howe [4] was used. This consists of: soy beans soaked over night, sterilized in autoclave 15 for forty-five minutes and mashed, 50 Gm.; rolled oats, 29 Gm.; butter, 5 Gm.; Fleischmann's yeast, 4 Gm.; dried milk (Klim), 10 Gm.; calcium carbonate, 1 Gm., and sodium chloride, 1 Gm. The ingredients are moistened, mixed thoroughly and spread in thin sheets to dry. Each guinea-pig was given 20 Gm. of the crumbled mixture daily, with filter paper for filler. In addition, each animal received 1 cc. of cod liver oil daily by medicine dropper. All animals were fed this basic diet plus 8 cc. of orange juice daily for one week, to accustom them to the food before the start of an experiment. The orange juice was withdrawn from all save the controls at this time. This diet produced definite signs of scurvy usually within from fifteen to twenty days, and if it was continued, death usually resulted within from twenty to forty days. Wolbach and Howe [4] and Wolbach [5] have reported on the effectiveness of this diet in producing a condition of total scurvy.

The diet productive of chronic scorbutic lesions given certain animals, as indicated below, consisted of the Wolbach diet plus 2 cc. of strained orange juice given by medicine dropper on every third day. This amount of the source of vitamin C was sufficient to maintain the weight of the animal and to cause no or only very slight gradual decrease in the red blood cell count and hemoglobin over a period of weeks. The deficiency did, however, prevent the normal rate of growth in the young, growing 300 to 400 Gm. animals used in this experiment. The semi-scorbutic diet administered to animals as listed in the table consisted of the diet productive of chronic scurvy with short periods of the diet causing acute scorbutic lesions. This was fed to determine whether variations in the severity of the deficiency might induce differences in the nature of the lesions.

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5. Wolbach, S. B.: Am. J. Path. **9**:689, 1933.

*Summary of Experimental Data*

| Animal | Dietary History | Infection History | Scurvy at Death* | Infection at Death† | Myocardial Lesions‡ | Degenerative Valvular Lesions¶ | Proliferative Valvular Lesions§ |
|---|---|---|---|---|---|---|---|
| | | **Animals on Diet Productive of Acute (Basal) Scurvy, with no Infection** | | | | | |
| 1 | Basal scorbutic diet to death in 30 days | None | +++ | 0 | 0 | ++ | ++ |
| 2 | Semiscorbutic diet 55 days; basal diet to death in 14 days | None | +++ | 0 | H | +++ | 0 |
| 3 | Basal scorbutic diet to death on 25th day | None | +++ | 0 | —H | +++ | +++ |
| 4 | Basal scorbutic diet 26 days, then semiscorbutic diet 26 days, then basal diet 14 days to death | None | ++ | 0 | 0 | +++ | + |
| 5 | Basal scorbutic diet to death on 21st day | None | +++ | 0 | 0 | +++ | +++ |
| 6 | Basal scorbutic diet to death on 41st day | None | +++ | 0 | ++H | +++ | +++ |
| 7 | Basal scorbutic diet to death on 24th day | None | +++ | 0 | + | +++ | +++ |
| 8 | Basal scorbutic diet to death on 22nd day | None | +++ | 0 | 0 | +++ | +++ |
| 9 | Basal scorbutic diet 68 days; only slight signs; animal killed | None | ++ | 0 | —H | +++ | 0 |
| 10 | Basal scorbutic diet to death on 44th day | None | +++ | 0 | ++H | +++ | +++ |
| | | **Animals on Diet Productive of Acute (Basal) Scurvy, with added Streptococcic Infection** | | | | | |
| 11 | Basal scorbutic diet to death on 40th day | G.-pig hem. strep.,‡ 24 hr. culture, 0.1 cc. intracutaneous, on 10th day; animal died 40th day | +++ | +++ | 0 | +++ | +++ |
| 12 | Basal scorbutic diet 10 days, semiscorbutic diet 67 days, then basal scorbutic diet 20 days to death on 97th day | G.-pig hem. strep., 24 hr. culture, 0.1 cc. intracutaneous, on 75th day | ++ | ++ | 0 | ++ | ++ |
| 13 | Basal scorbutic diet to death on 20th day | G.-pig hem. strep., 0.1 cc. intracutaneously on 11th day | +++ | +++ | H | ++ | + |
| 14 | Basal scorbutic diet to death on 50th day | 195H human hem. strep., increasing weekly injections | +++ | +++ | 0 | ++ | 0 |
| 15 | Basal scorbutic diet to death on 23rd day | H30 human strep. on 7th day and large injection 24 hr. before death | +++ | +++ | —H | +++ | +++ |
| 16 | Basal scorbutic diet to death on 39th day | NY5 Dochez hem. strep. agar focus on 10th day | ++ | +++ | 0 | ++ | 0 |
| 17 | Basal scorbutic diet to sudden convulsive death on 35th day | H30 human hem. strep. agar focus on 20th day; death from convulsions | ++ | + | 0 | ++ | ++ |
| 18 | Basal scorbutic diet to death on 35th day | NY5 Dochez hem. strep. agar focus on 17th day | +++ | +++ | +++H | +++ | ++ |
| 19 | Basal scorbutic diet to death on 36th day | NY5 Dochez hem. strep., 0.1 cc. intracutaneously on 15th day | +++ | + | 0 | ++ | 0 |
| | | **Animals on Semiscorbutic Diet, with Added Streptococcic Infection** | | | | | |
| 20 | Semiscorbutic diet to death on 67th day | G.-pig hem. strep., 0.1 cc. intracutaneously on 12th day; lesion subsided; injection repeated on 57th day | +++ | ++ | 0 | +++ | +++ |
| 21 | Basal scorbutic diet 9 days, semiscorbutic diet to death on 29th day | 19H human hem. strep., 0.1 cc. intracutaneously on 12th and 14th days | +++ | + | H | +++ | +++ |
| 22 | Semiscorbutic diet 64 days, then basal diet 7 days, then semiscorbutic diet 18 days to death on 86th day | NY5 Dochez hem. strep. toxin, 1 cc. intraperitoneally on 65th day; repeated on 85th day; animal killed on 86th day | ++ | 0 | 0 | +++ | ++ |
| 23 | Semiscorbutic diet 79 days; no orange juice last week; animal went rapidly to death on 86th day | H30 human hem. strep. agar focus on 47th day | +++ | + | —H | ++ | + |
| 24 | Semiscorbutic diet to death on 71st day | H30 human strep. agar focus on 47th day | +++ | + | 0 | +++ | ++ |
| 25 | Semiscorbutic diet to death on 21st day | NY5 Dochez hem. strep. agar focus on 13th day | ++ | +++ | 0 | ++ | 0 |
| 26 | Semiscorbutic diet 45 days, then basal diet 7 days, and back to semiscorbutic for 14 days to death on 66th day | NY5 Dochez hem. strep. agar focus on 10th day | +++ | ++ | H | +++ | ++ |
| 27 | Basal scorbutic diet for 28 days, then 5 cc. orange juice daily for 5 days, and back to semiscorbutic diet for 36 days to death on 69th day | NY5 Dochez hem. strep. agar focus on 14th day | ++ | ++ | 0 | +++ | + |
| | | **Animals on Adequate Diet, with Streptococcic Infection** | | | | | |
| 28 | Normal diet to death on 32nd day after injection of organisms | G.-pig hem. strep., 24 hr. broth culture, 0.1 cc. subcutaneously | 0 | +++ | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| of organisms | | G.-pig hem. strep., 24 hr. broth culture, 0.1 cc. subcutaneously | 0 | +++ | 0 | 0 | 0 |
| 29 | Normal diet to death on 46th day after injection of organisms | G.-pig hem. strep., 24 hr. broth culture, 0.1 cc. subcutaneously | 0 | +++ | 0 | 0 | 0 |
| 30 | Normal diet to death on 28th day after injection of organisms | G.-pig hem. strep., 24 hr. broth culture, 0.1 cc. subcutaneously | 0 | +++ | 0 | 0 | 0 |
| 31 | Normal diet to death on 37th day after injection of organisms | G.-pig. hem. strep., 24 hr. broth culture, 0.1 cc. subcutaneously | 0 | +++ | 0 | + | 0 |
| 32 | Basal scorbutic diet and 8 cc. orange juice daily to death on 23rd day | G.-pig strep., 24 hr. broth culture, 0.1 cc. intracutaneously on 15th day | 0 | +++ | 0 | 0 | 0 |
| 33 | Basal scorbutic diet and 8 cc. orange juice daily until killed on 67th day | G.-pig strep., 24 hr. broth culture, 0.1 cc. intracutaneously on 10th day; repeated on 30th and 45th day | 0 | ++ | 0 | 0 | 0 |
| 34 | Basal scorbutic diet and 8 cc. orange juice daily until killed on 98th day | 195H human hem. strep., broth culture, 0.2 cc. intracutaneously on 10th day; repeated 15th day; 100 × concentration given 38th day and repeated 70th day; agar focus 80th day | 0 | + | 0 | 0 | 0 |
| 35 | Basal scorbutic diet and 8 cc. orange juice daily killed on 93rd day | H30 human hem. strep., broth culture, 0.2 cc. intracutaneously 10th day; agar focus 43rd day | 0 | + | 0 | + | 0 |
| 36 | Basal scorbutic diet and 8 cc. orange juice daily until death on 74th day | NY5 Dochez hem. strep. agar focus on 5th day | 0 | + | ++ | 0 | 0 |
| 37 | Basal scorbutic diet and 8 cc. orange juice daily until death on 68th day | G.-pig hem. strep., 24 hr. broth culture, 0.1 cc. intracutaneously on 5th, 30th and 60th day | 0 | +++ | 0 | 0 | 0 |

* The symbols used have significance as follows:
0 No gross or microscopic evidence of scurvy.
+ No gross evidence of scurvy, but microscopic evidence of scurvy.
++ Three or more mild clinical signs and gross evidence of scurvy (as mild hemorrhage and slight joint or epiphysial change).
+++ Most or all of the clinical signs of severe scurvy with widespread hemorrhage and other pathologic evidence of severe scurvy (I. e., loose, defective teeth, multiple joint involvement and typical epiphysial changes of scurvy).

† The symbols used have the following significance:
0 No evidence of infection.
+ Single well localized abscess.
++ Large, poorly localized abscess with involvement of one or more regional nodes.
+++ Widespread multiple abscesses or generalized nonlocalized streptococcic infection with or without septicemia.

‡ In this study the organisms used are designated as follows:
G.-pig hem. strep. A hemolytic streptococcus isolated from a spontaneous epidemic of lymphadenitis in guinea-pigs. It was quite virulent when first isolated but much less so during the progress of the experiment.
195H. A hemolytic streptococcus isolated from a patient with acute pharyngitis and carried in stock culture for a year before use.
H30. A hemolytic streptococcus isolated from a patient with acute pharyngitis and carried in stock for two years before use.
NY5. The Dochez strain of the so-called scarlatinal hemolytic streptococcus.
Agar foci were made by making 1:10 to 1:15 dilutions of a twenty-four hour broth culture in warm nutrient agar and injecting from 1 to 2 cc. into the groin subcutaneously while the agar was still liquid. All cultures were twenty-four hour transfers in phosphate-buffered 0.3 per cent dextrose beef infusion broth, $p_H$ 7.6.

# The symbols used have the following significance (Hemorrhage is designated as H):
0 Normal myocardium. The slight subendocardial and myocardial mononuclear cell and lymphocytic cell accumulations seen in most normal guinea-pigs are considered to be normal.
+ A few small foci of myocardial degeneration with lymphocytic and phagocytic cell infiltration. Some of these areas show evidence of old hemorrhage.
++ A moderate number of medium-sized foci of myocardial degeneration with moderate infiltration by mononuclear phagocytic cells, some of which contain blood pigment. There is also a definite proliferative reaction on the part of fibroblastic cells, with no formation of intercellular substance.
+++ Widespread fusiform areas of myocardial degeneration with lymphocytic and large mononuclear cell infiltration and marked proliferative reaction with attempted organization.

¶ Degenerative changes, if present, usually affect all the valves to some extent, but usually with decreasing severity in the following order: (1) aortic, (2) mitral, (3) tricuspid, (4) pulmonary. The symbols used have significance as follows:
0 Normal, compact, uninterrupted fibrillar connective tissue structure with a normal number of mature-looking fibroblasts; lining endothelium normal.
+ A loose fibrous stroma with slight interruption of the connective tissue fibrils but with normal staining reaction and no cellular infiltration and no proliferation of either stroma cells or endothelial lining cells.
++ Apparent edema of the valve structure and decrease in the fibrillar structure, with change in the staining reaction and disorientation of the connective tissue fibrils.
+++ Marked edema and thinning of connective tissue structure with marked fragmentation and disorientation of collagen fibers; commonly, pyknosis in some of the fibroblastic cells.

§ The proliferative valvular lesions usually were observed at the line of closure of the valve. The symbols used have meanings as follows:
0 No proliferative reaction.
+ A slight reaction with proliferation of the endothelial lining cells, first evidenced by change from flat to basophilic cuboidal endothelium; sometimes a slight lymphocytic and large phagocytic cell infiltration.
++ A definite moderate proliferative reaction of endothelial cells, as evidenced by palisading and basophilia; also proliferation of the underlying stroma cells, with an infiltration of lymphocytes and large phagocytic cells; commonly, the presence of somewhat necrotic looking material of hyaline nature in these underlying lesions.
+++ One or more large nodular reactions with marked proliferation of endothelial lining cells and an evident reaction in the underlying stroma cells, consisting of proliferation, occasional mitoses, lymphocytic infiltration, and a few polymorphonuclear cells, numerous large phagocytic cells and occasional multinucleate cells. There are definite amounts of hyaline necrotic-looking material in the areas concerned.

## Explanation of Plate 1

Fig. 1 (guinea-pig 12, diet as in table).—Aortic valve; hematoxylin and eosin stain; × 50. Note edema and fragmentation of the collagen of one aortic valve leaflet. There is minimal proliferative reaction.

Fig. 2 (guinea-pig 8, basal diet to death on twenty-second day).—Mitral valve; hematoxylin and eosin stain; × 35. The valve is generally thickened. The darker area to the left represents acute valvulitis with hemorrhage and polymorphonuclear leukocytic and lymphocytic infiltration.

Fig. 3 (guinea-pig 5, basal diet to death on twenty-first day).—Mitral valve; hematoxylin and eosin stain; × 30. The valve is definitely thickened with a proliferative nodule at the line of closure.

Fig. 4 (guinea-pig 5, basal diet to death on twenty-first day).—Mitral valve; hematoxylin and eosin stain; × 200. This is a high power view of a proliferative nodule at the line of closure of the valve. Note the proliferation of endothelial and subendothelial cells. Phagocytic cells, lymphocytic and other mononuclear cells are distinguishable.

Fig. 5 (guinea-pig 7, basal diet to death on twenty-fourth day).—Mitral valve; hematoxylin and eosin stain; × 30. Note the definite small proliferative nodule at the line of closure. The general thickening and edema are minimal.

Fig. 6 (guinea-pig 7, basal diet to death on twenty-fourth day).—Mitral valve; hematoxylin and eosin stain; × 150. Note the proliferative nodule at the valve's line of closure. The nodular character is definite, with proliferation of subendothelial and stroma cells. A few lymphocytes are present.

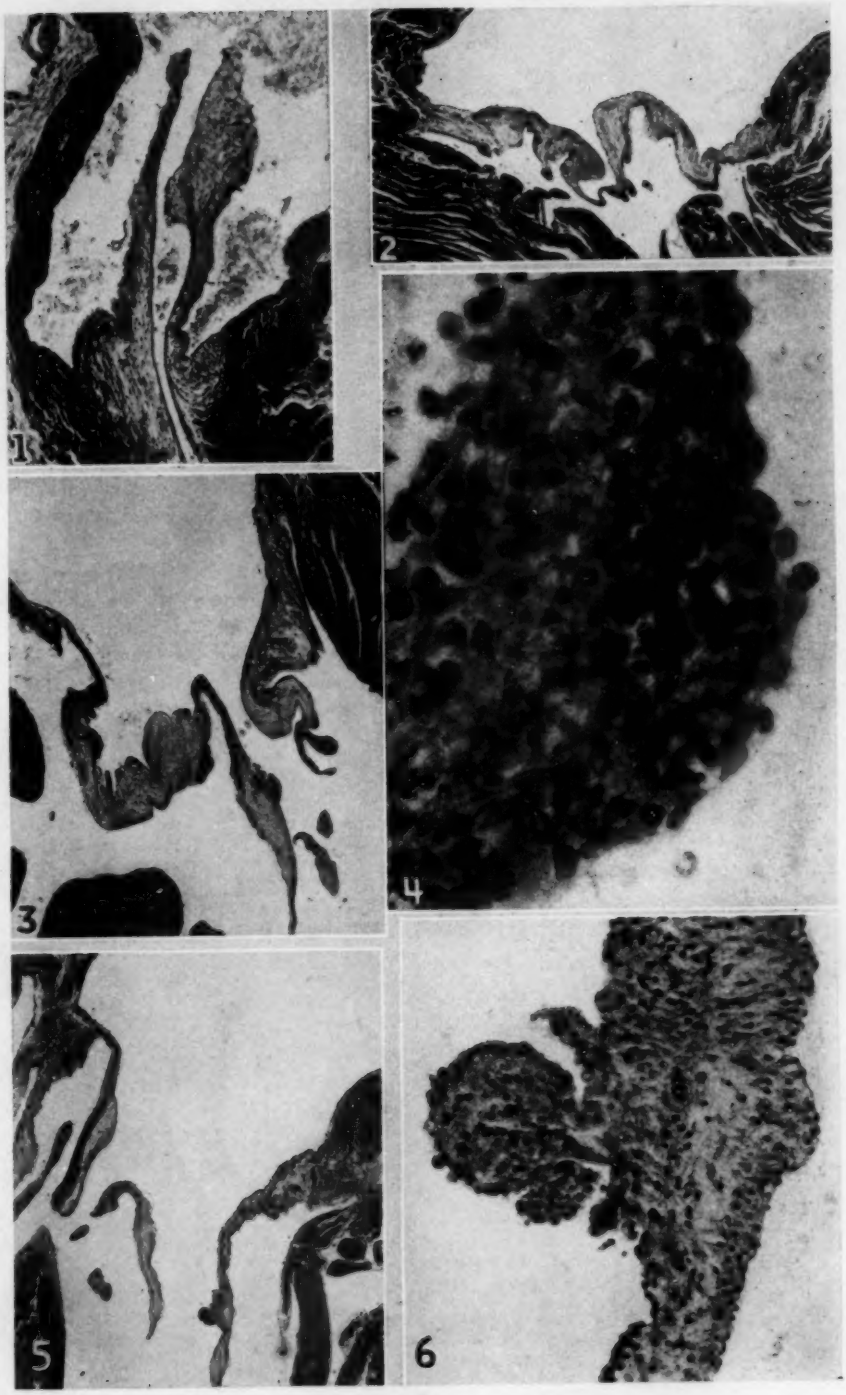


Figure 1

EXPLANATION OF PLATE 2

Fig. 1 (guinea-pig 6, basal diet to death on forty-first day).—Mitral valve; hematoxylin and eosin stain; × 30. There is a marked proliferative nodular reaction at the line of closure on each valve leaflet. This is more definite on the right.

Fig. 2 (guinea-pig 6, basal diet to death on forty-first day).—Mitral valve; hematoxylin and eosin stain; × 150. Fibroblastic proliferation is present, and some collagen change and débris are distinguishable. Lymphocytic infiltration is evident, as is edema of the valve stroma at the lower end of the figure.

Fig. 3 (guinea-pig 8, basal diet to death on twenty-second day).—Mitral valve; hematoxylin and eosin stain; × 30. There is marked edema of the entire valve stroma with definite thickening of the valve and an acute reaction at the line of closure.

Fig. 4 (guinea-pig 8, basal diet to death on twenty-second day).—Mitral valve; hematoxylin and eosin stain; × 150. The acute valvulitis and proliferative reaction at the line of closure are evident. Edema and the poor structure of the collagen are well demonstrated. Lymphocytic and phagocytic cell infiltration may be made out with ease.

Fig. 5.—Normal aortic valve; hematoxylin and eosin stain; × 50.

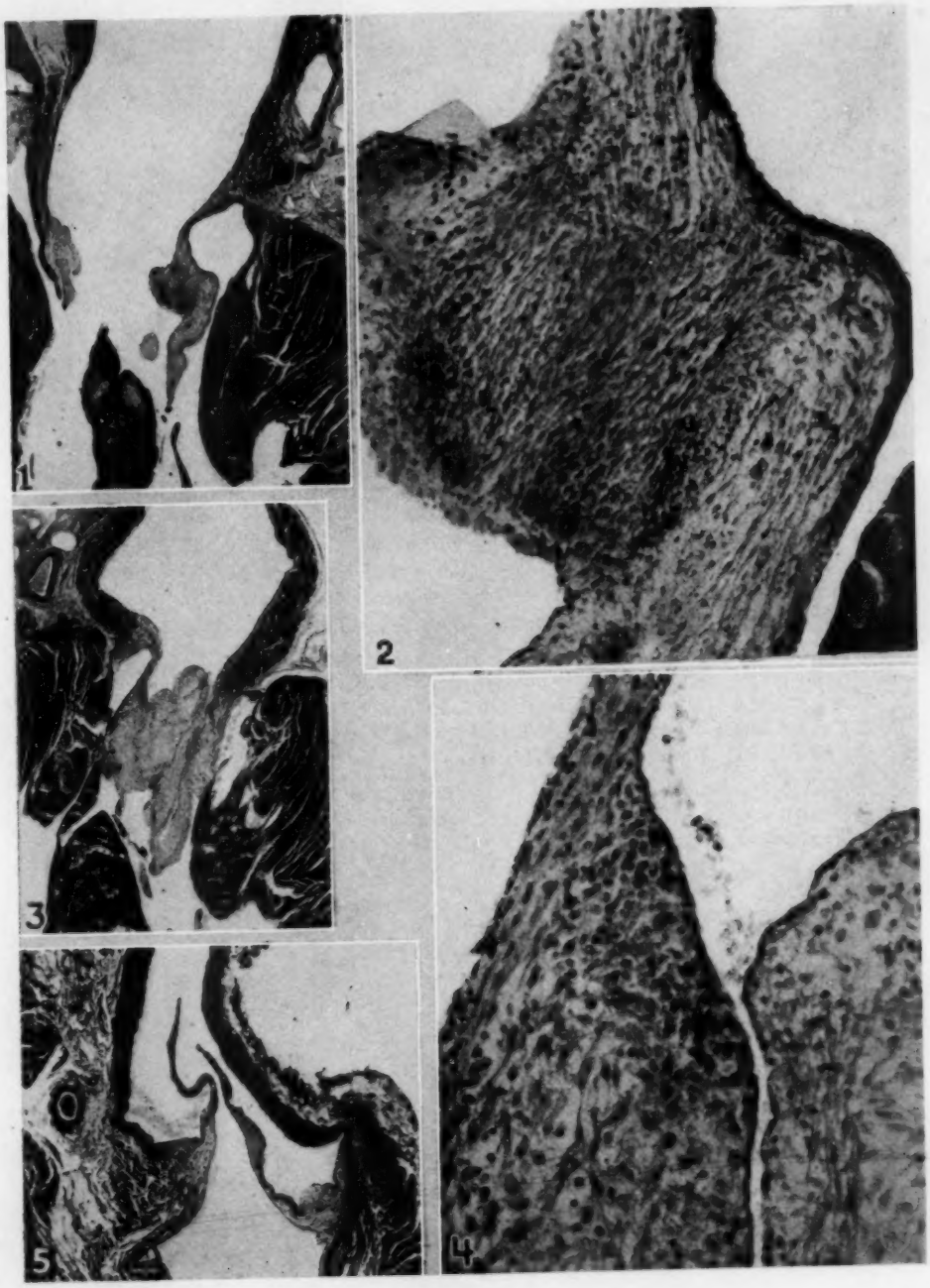


Figure 2

## Explanation of Plate 3

Fig. 1 (guinea-pig 3, basal diet to death on twenty-fifth day).—Mitral valve; hematoxylin and eosin stain; × 125. There is marked edema of the valve (lower portion of the picture) with disruption of the normal collagen structure. The proliferative nodular reaction at the line of closure in the left center is well shown. A slight lymphocytic reaction of the whole area is present.

Fig. 2 (guinea-pig 10, basal diet to death on forty-fourth day).—Myocardium; hematoxylin and eosin stain; × 250. Myocardial degeneration is well demonstrated, as is some edema. The cellular reaction is not marked and is almost entirely limited to large mononuclear cells of undifferentiated type with some phagocytic wandering cells.

Fig. 3 (guinea-pig 20, semiscorbutic diet to death on sixty-seventh day with added streptococcic infection as indicated in table).—Mitral valve; hematoxylin and eosin stain; × 440. A high magnification of a nodule showing endothelial and subendothelial proliferation. This is an unusually marked reaction of the type.

Fig. 4 (guinea-pig 21, diet and infection as in table).—Mitral valve; × 150. Increased thickness of the valve is apparent, as is the nodular area of cellular proliferation and infiltration. The cells involved are endothelial lining cells and underlying fibroblasts, with an infiltration of lymphocytes and phagocytic wandering cells.

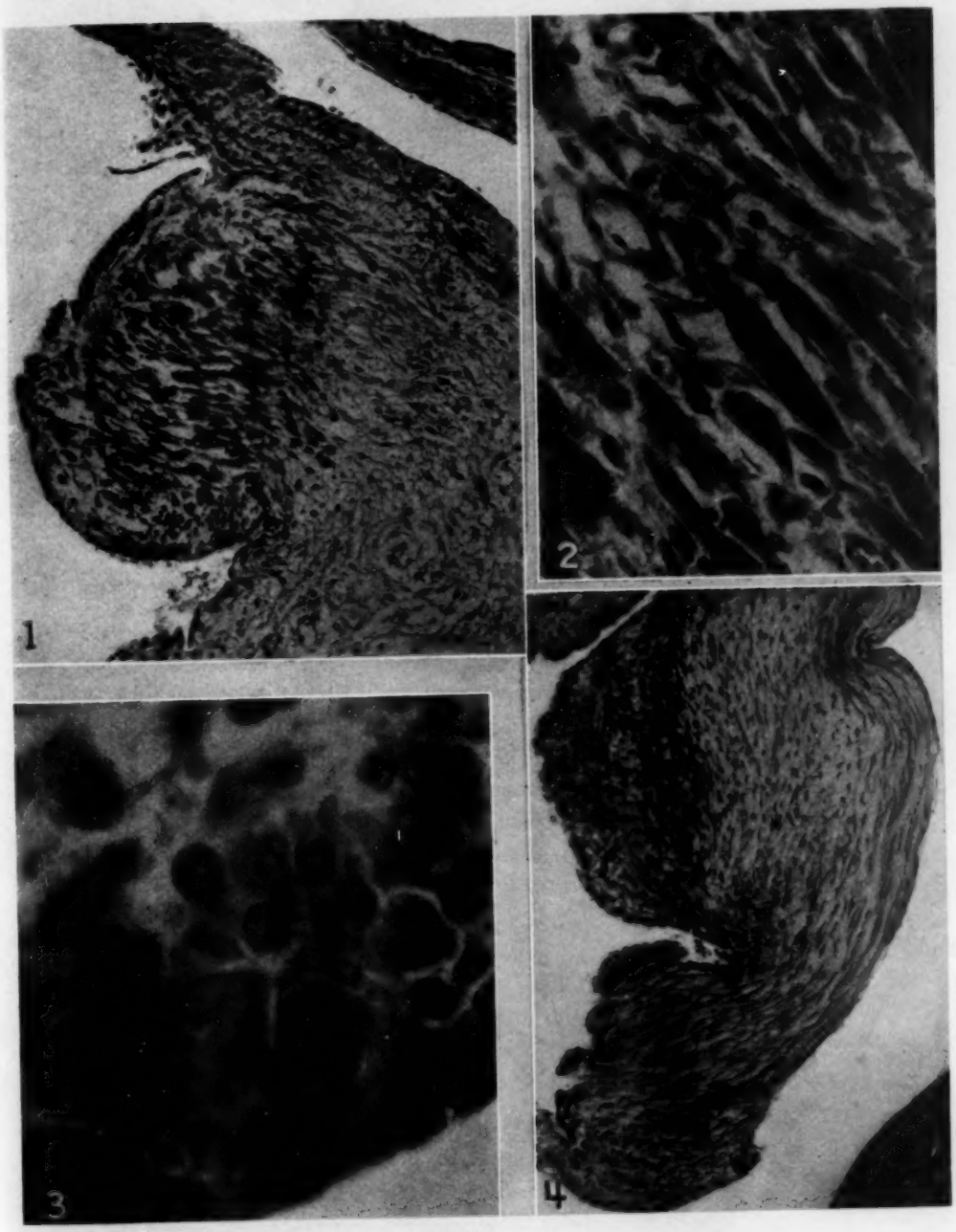


Figure 3

Symptoms and signs considered as indexes of scurvy in this study are: (*a*) loosening of upper or lower incisor teeth; (*b*) hemorrhage from the gums; (*c*) limitation of motion and sometimes swelling of joints; (*d*) continued loss of weight in absence of other causes; (*e*) a marked drop in the red blood count and in the hemoglobin content. Pathologic changes considered indicative of scurvy are: (*a*) widespread hemorrhagic phenomena, which may occur in almost any portion of the body, but particularly in the rear extremities in and about joints, in muscles and subperiosteally; (*b*) hypoplasia of erythropoietic tissue; (*c*) thinning of the cortical structure of bones; (*d*) interruption of growth at epiphysial junctions and failure to lay down intercellular substance, with hemorrhage into the area occurring quite frequently; (*e*) defective growth of teeth.

A count of the red blood cells and a determination of hemoglobin by the Sahli method were performed on each animal each week, at which time the animal was also weighed. It was examined at frequent intervals for signs of scurvy, and for its condition if it was one of those with infection. Every animal was given complete bacteriologic and pathologic examinations at death. The results of the present study are concerned only with the changes in the heart. Each heart was serially sectioned and every third slide stained with hematoxylin and eosin for examination. The other slides were kept for special stains as indicated.

Young, growing males, weighing from 300 to 400 Gm. at the start of the experiment, were used and divided as follows:

(*a*) 10 guinea-pigs on a diet productive of acute (basal) scurvy, without any infection

(*b*) 9 guinea-pigs on a diet productive of acute (basal) scurvy, with added hemolytic streptococcic infection

(*c*) 8 guinea-pigs on a semiscorbutic diet, with superimposed hemolytic streptococcic infection

(*d*) 10 guinea-pigs on a normal or control diet, with hemolytic streptococcic infection

It is appreciated that the number of animals used in this study is small for a dietary experiment, but, in the first place, the results are consistent, and, in the second place, an attempt was made simply to demonstrate whether or not the lesions occur in the acutely scorbutic heart with or without superimposed streptococcic infection.

## RESULTS

The results are presented in tabular form for the sake of brevity and clarity (table). This form, with brief descriptions, is used in this paper because the lesions, so far as can be determined, are identical with those which have been adequately described by Rinehart and Mettier.[1]

## COMMENT

From the results shown in the table it is evident that degenerative and proliferative valvular lesions of marked degree are found in a majority of guinea-pigs that die in a condition of acute scurvy. These lesions are equally prevalent and severe whether or not there is superimposed streptococcic infection. The animals on a semiscorbutic diet with a superimposed infection showed at autopsy evidence of acute scurvy. The microscopic lesions were essentially the same as those seen in acute scurvy alone or in acute scurvy plus infection.

In the myocardium of animals in an acute scorbutic condition, focal hemorrhage is common. In addition, there are areas of focal myocardial degeneration with some proliferative reaction, as already described. Since in many of these areas there are phagocytic cells filled with hemosiderin, red cells and apparent fibroblasts, these lesions are interpreted as an attempt at organization of a previous hemorrhage.

Rinehart and Mettier [1] reported striking differences in the frequency and severity of the lesions as between infected and noninfected scorbutic animals. In the present study no such differences were observed.

In the present work the diet of Wolbach and Howe [4] was used, since Wolbach [5] demonstrated its efficiency in producing the total picture of pure scorbutus.

In view of the findings and differences, therefore, it seems possible that the diet used by Rinehart and Mettier was capable of producing only moderately severe scurvy and required added infection to produce total scurvy. It is a common clinical observation that infection is often a precipitating factor in acute scorbutus in human beings.

A deficiency of vitamin C, as shown by Wolbach and Howe [4] and Wolbach,[5] prevents the adequate formation and maintenance of intercellular substance. It may be expected, therefore, that in regions of strain and stress degenerative lesions may occur, and that a proliferative reaction may take place in an attempt at repair. It is as such that the lesions produced in the present study are interpreted.

The complete gross and microscopic pathologic changes of rheumatic fever are obviously dissimilar from those of scurvy, even though in some of the microscopic lesions of the valves in both conditions there are certain points in common: a subendothelial proliferative reaction with a cellular infiltration and a collagen change. There is also damage to the vascular system in both conditions, but the identity of this injury has not been demonstrated. Although scurvy may indirectly be a factor in lowering the general resistance of the body to infection, there is as yet no evidence that rheumatic fever and scurvy are the same disease, or that there is a direct causal relationship between the two, even with

infection by the hemolytic streptococcus complicating the latter. The lesions in the guinea-pig heart described by Rinehart and Mettier may be produced by acute scurvy alone and may be interpreted as an attempt at repair of lesions caused by physiologic stress on a tissue weakened by acute scorbutus.

## SUMMARY

Acute scurvy in the guinea-pig produces degenerative changes in the cardiac valves and myocardium as well as definite proliferative lesions along the line of closure of the valves. These lesions are equally prevalent and severe in total scurvy whether or not there is superimposed infection.

# THE SIZE OF THE SPLEEN AND THE LIVER-SPLEEN RATIO

## A STATISTICAL STUDY BASED ON ONE THOUSAND AUTOPSIES

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The present study represents an attempt to treat statistically the variations in the size of the spleen in respect to sex, age, body length and body type and in conjunction with various diseases. In carrying out this primary purpose it is necessary to ascertain a so-called normal size of the spleen, with which the size of the organ under varying conditions may be compared. The approximate degree of variation is expressed by means of a ratio, and finally the degree of deviation in the size of the liver in relationship to that of the spleen is computed. This investigation is undertaken in the hope that more exact knowledge of the correlation between splenic size and certain normal and abnormal states of the body will be found to be of value in differential diagnosis. Through such studies the mass information of a large series of autopsies may be made available to the clinician for application in the particular diagnostic problems of his individual patient.

### PREVIOUS INVESTIGATIONS

Since the size of the spleen is influenced by a large number of factors, variable in the human body, it is not surprising that the values found by different investigators, who have approached this problem from diverse angles, have shown wide differences. This applies especially to the values for normal spleens. Lubarsch [1] cited a number of writers who proposed values for the normal spleen ranging between 115 and 300 Gm. Lubarsch [1] himself expressed the belief that on the average a weight of 150 Gm. should be considered normal. Greenwood [2] divided a very large material into two groups, which he investigated as to splenic weight. The mean value of the splenic weight in his "general hospital population" he found to be 187.39 Gm., and that in his "selected cases with normal hearts," 148 Gm. (The figures were given in ounces but have been changed to grams for easier com-

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From the Department of Pathology of the University of Michigan.

1. Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, vol. 1, pt. 2.

2. Greenwood, M.: Biometrica **3**:63-83, 1904.

parison.) Moon [3] found an average of 144.74 Gm. for 1,000 white patients after excluding those having diseases known to affect the size of the spleen. The corresponding value for 1,000 Negro patients was 100.25 Gm. Vierordt,[4] in his tables on growth of organs, stated the normal adult splenic weight as 163 Gm. In another table,[5] which differentiates between the sexes and between various ages, he reported the following figures for the weight of the normal spleen: in males, at 15 years of age, 145 Gm.; at 20 years of age, 186.2 Gm., and at 25 years of age, 163 Gm. In females, at 15 years of age, 121.7 Gm.; at 20 years of age, 145.6 Gm., and at 25 years of age, 173.3 Gm. He did not mention how these figures were obtained or on how large a material they were based.

Greenwood [2] divided his material into three age groups and found splenic weights as follows: at from 25 to 35 years, 211.2 Gm.; at from 35 to 45 years, 187.1 Gm., and at from 45 to 55 years, 176.05 Gm. Inspection of these figures, as well as of those of Vierordt, indicates variations so marked between closely similar age groups that it does not seem possible that these figures can be based on any large number of normal persons.

Pearl and Bacon [6] found the weight of the spleen to become progressively larger as age advances, up to the decade centering at 35 years, and to become progressively smaller at the more advanced ages thereafter. They agreed with previous writers that the absolute weight of the spleen is definitely greater in the white than in the colored group. Making use of the data collected by Oppenheimer [7] on those dying as a result of accident, Pearl and Bacon computed the mean weight of the spleen in the age group centering about 25 years to be 164.8 Gm. for males and 160.7 Gm. for females.

Moon [3] found a general tendency to decreasing splenic weight in adults of eight decades of life, beginning at 19 years of age, and of both sexes, the spleens of females being slightly smaller than those of males of corresponding age groups.

The literature on the size of the spleen in various diseases is not abundant. Barron and Litman,[8] who based their report on an autopsy series of 12,000 cases, of which about 9,000 were utilized, gave the

3. Moon, V. H.: Arch. Path. **5**:1040-1043, 1928.

4. Vierordt, H.: Anatomische, physiologische und physikalische Daten und Tabellen zum Gebrauche für Mediciner, Jena, G. Fischer, 1893.

5. Vierordt, H.: Arch. f. Anat. u. Entwcklngsgesch., supp., 1890, pp. 62-94.

6. Pearl, R., and Bacon, A. L.: Johns Hopkins Hosp. Rep. **21**:297-377, 1921-1924.

7. Oppenheimer, Carl: Ztschr. f. Biol. **25**:328-357, 1889.

8. Barron, M., and Litman, A. B.: Arch. Int. Med. **50**:240-256, 1932.

distribution, by intervals of 50 Gm., of all spleens encountered which exceeded 300 Gm. and arranged these according to the primary causes of death. They found marked enlargement of the spleen in cirrhosis of the liver, leukemia, Hodgkin's disease and amyloidosis; a moderate enlargement of the spleen in heart disease, acute infections, traumatic conditions, septicemia and subacute bacterial endocarditis. They found marked enlargement of the liver in carcinoma, melanoma and amyloidosis; moderate enlargement of the liver, in heart disease, acute infections, traumatic conditions, alcoholism, septic abortion, subacute bacterial endocarditis, leukemia and Hodgkin's disease.

Greenwood [2] found that in pneumonia the spleen has an average weight of 186.8 Gm.; in heart disease, 242.95 Gm. Pearl and Bacon [6] gave a very complete biometric analysis of splenic weight in tuberculosis. They concluded that, although the question must be left open, there does not appear to be a significant difference in the absolute weight of the spleen in tuberculous and nontuberculous persons. Moon [3] mentioned in his study on racial differences of splenic weight that acute infections cause no great splenic enlargement. Bean [9] reported on the weight of the spleen and other organs in relation to type, race, stature, sex and age. He did not state, however, the exact weights, but concluded that the organs are smaller in hyperontomorphs than in comparable meso-ontomorphs and larger in white males than in comparable Negro males. He found that in respect to size the spleen is affected by age to a greater degree than any other organ.

## MATERIAL UTILIZED IN THE PRESENT STUDY

The present material consists of 1,000 cases selected at autopsies performed in the department of pathology of the University of Michigan. These were not consecutive cases, since only those of persons who had acquired approximately adult stature were included. The youngest person was a girl 12 years of age; the oldest, a man of 88 years. Furthermore, certain cases were arbitrarily included in order to secure a more adequate representation of certain disease states. The individual case has been classified according to pathologic diagnosis, sex, age, splenic weight, hepatic weight, body stature and body type. Forty-seven diseases are found to be represented by groups of from 1 to 173 cases. If in any case several conditions were diagnosed, the principal pathologic condition or the primary cause of death has been chosen for purposes of classification. The forty-seven diseases are grouped together into nine large disease groups, of which only four can be discussed thoroughly; two more will be considered chiefly in

9. Bean, R. B.: Anat. Rec. **11**:326-328, 1916-1917.

respect to splenic weight in its relation to sex and to the weight of the liver, while the three remaining groups, in each of which the number of cases is small, will serve for comparative purposes only.

The various items will be discussed in relation to splenic weight, as weighing appears to be the most accurate way of expressing the size of an organ. Determining the size by computing the volume from the length, width and thickness is not favored on account of the following considerations:

1. In the procedure of autopsy, weighing is more accurately performed than measuring.

2. Multiplying the values for length, breadth and thickness yields a product which expresses, not the exact volume, but a value which stands in a rather constant proportion to the actual volume. It might be sufficiently accurate if the data given by the prosectors were exact to millimeters. As these figures are given ordinarily only in centimeters and half centimeters, the resulting magnification of a seemingly trivial error by its introduction in a series of three factors may make a gross error in the product.

3. No other organ in the body shows greater variability in shape than does the spleen. The assumption that the product of the multiplication of the three diameters is a usable basis for comparison is especially unsound with respect to the spleen. This may be demonstrated by the following experimental procedure: with 200 cc. of modeling clay a model of a spleen is formed, measuring 12 by 7 by 3 cm., figures which are the approximate means for the diameters of normal spleens as given by various anatomists (cited from Lubarsch). This model represents a practically normal spleen of almost quadrangular cross-section, the product of multiplying the values for the length, width and thickness being 252. Now the same mass (and therefore the same volume) of modeling clay may be changed into the shape of a soft, flabby, flat spleen, measuring 16.4 by 8.7 by 2.1 cm.: These diameters multiplied yield the product 299.63. Again a mass of clay having a volume of 160 cc. may be formed into another spleenlike solid of the same diameters as the first, 12 by 7 by 3 cm., with a product of 252, this time representing a spleen of more triangular cross-section. This model may be changed into the shape of a flat spleen having the measurements 15.2 by 7 by 2, which yield the product 212.8. In the two instances, although the volume of the clay was constant, the products of the multiplication of the values for the length, breadth and thickness differed by 19 per cent above and 15 per cent below the original product 252.

For these reasons only splenic weights are used in this investigation.

## SOURCES OF ERROR IN MATERIAL AND METHODS

The following sources of error are inherent in the material as utilized: The subdivision of the material into various small groups results in too few cases in some groups to be statistically significant. The larger disease groups include diseases which themselves may differ largely in respect to splenic size. The disease picture in a given instance may include two or more disease entities which may have been antagonistic or synergistic in respect to influencing splenic size. In a single disease group the disease is not uniform in itself, as in some cases it may

show advanced and in others only early stages, resulting in variable effects on the size of the spleen. The weight of the spleen is dependent to a certain extent on the amount and the fluidity of the blood. This fact is not considered in the usual autopsy routine, and the organ may be more or less completely "bled out" at the time of weighing.

### DETERMINATION OF NORMALITY

As the present investigation deals primarily with comparisons, it is first necessary to establish a basis of normality in splenic size for the material at hand. The review of the literature has shown that no organ has a greater variability in respect to normal size than has the spleen, as the data on normal splenic size given by several authors varied between 115 and 300 Gm. The reason for this discrepancy lies in the fact that every fatal condition will, or at least might, cause change in the size of the spleen. A normal spleen in the narrowest sense can be found only in an absolutely healthy young or early middle-aged person who has suffered traumatic death not more than twenty-four hours after injury, and death that was not due to exsanguination or infection. As such a material sufficiently large for statistical purposes can be found only under very special conditions, a basis of normality for the present material has to be determined by segregating a group of cases in which normal spleens were to be anticipated. The elements of this group are not entirely free from criticism, some diseases having been admitted which would have no place in a series in which an effort was being made to obtain the mean weight of absolutely normal spleens rather than a basis for comparison. In this so-called normal group all cases are included in respect to which there were no known reasons to expect splenic enlargement whether the splenic weights exceeded the norm or not. For instance, the largest spleen in this group weighed 510 Gm., a weight undoubtedly far above the average; but, as this spleen was from a person who suffered traumatic death and was without evidence of disease that would lead one to expect enlargement of the spleen, it was included in this group.

The average splenic weight of 177.5 Gm. (the mean of the splenic weights in the 177 cases included in group 1) will be regarded as the normal weight of the spleen for this material and as the basis for the comparative studies. I wish to make it clear that this value is not proposed as the mean weight of the rigidly defined absolutely normal spleen. I believe that the value obtained is probably slightly above the true norm, notwithstanding the fact that diminution in splenic size, which plays a minor rôle, was not considered in securing the figures.

Although the classification of the forty-seven diseases into nine disease groups is done primarily from the point of view of the spleen,

the mean hepatic weight in disease group 1, 1,650.9 Gm., is considered to represent the norm of this material for purposes of comparison. The limitations as to the accuracy of this normal value are the same as apply to that of the normal splenic weight but are probably less significant.

Table 1 presents the data on the material selected from 1,000 autopsies, grouped under forty-seven disease titles and classified accordingly into nine major groups. For each disease the number of cases, their distribution as to sex and the average age of the patients are stated. The extremes of the weights of the spleen and liver, the mean value of these weights and the standard deviation are tabulated. Finally, to be discussed later, the liver-spleen ratio and the deviation ratio of the spleen and of the liver are given in each instance.

### MEAN VALUES AND STANDARD DEVIATIONS

It will be noted that in the other eight groups the mean weight of the spleen is, in every instance, higher than the so-called normal splenic weight of group 1. Only the weight in malignant neoplastic conditions closely approaches the so-called normal weight. It is to be noted that the standard deviation of the splenic weight is remarkably high in all of the major disease groups, being usually higher than one half of the mean weight of the spleen for the group concerned. In lymphoblastoma it is even far above the mean, indicating that the value of 744.6 as the average splenic weight in lymphoblastoma is of mathematical rather than clinical significance. One has to expect such a high standard deviation in the lymphoblastoma group as defined here, since this group contains not only the huge spleens of patients with myelogenous leukemia but also the spleens of those with multiple myeloma and those with mycosis fungoides, which range relatively close to the norm. A consideration of the standard deviation of the splenic weight in these groups in connection with the number of cases in each group gives an indication of the probable extent of deviation from the computed value to be expected in a spleen of this group as encountered clinically. In contrast to the splenic mean weight is the hepatic mean weight so far as variability is concerned, for here the standard deviation seldom exceeds one fifth to one fourth of the mean weight of the liver. Only in one instance, in disease group 9, does it exceed one half of this value.

### DEVIATION RATIOS OF SPLEEN AND LIVER

In order to express numerically the deviation in the size of the spleen and of the liver from the norm, the mean values of splenic and hepatic weights for each disease and for each disease group were

divided by the normal values, 177.5 and 1,680.9, respectively. The quotients thus obtained are called the deviation ratios of the spleen and liver. Values below 1 indicate, therefore, diminution in size; those above 1, enlargement, and the value of 1, no change in size for the disease or disease group in question. It is obvious that this method may be applied not only to diseases and disease groups but also to individual cases. The computed ratios appear in table 1. They show that:

1. A diminution in the size of a spleen or of a liver is of but little importance in material such as this if the groups considered contain a sufficiently large number of cases. This conclusion is on less firm ground here than it would have been, however, had it not seemed desirable to include in the so-called normal group conditions which may produce diminution in the size of the spleen.

2. Only one of the groups (besides group 1, the value of which is unity by definition) has a splenic deviation ratio which is practically normal, while three of the groups show hepatic deviation ratios which are equal or almost equal to that of group 1.

3. The ratios of the spleen deviate not only more often but also to a greater magnitude than do those of the liver. While the former reach 3 and 4, the latter remain below 1.4, except for the single small group in which metastatic neoplasms were present in the spleens. In this group the hepatic deviation ratio is 1.99, while the corresponding splenic value is 1.66. In general, however, these ratios demonstrate a greater variability in the size of the spleen than in that of the liver under the influence of a large variety of disease conditions.

### DISEASES ASSOCIATED WITH DIFFERENT SIZES OF THE SPLEEN

*Small Size.*—Table 1 shows in general that the following diseases are associated, on the average, with small size of the spleen (below 160 Gm.):

Tumor of the brain
Bronchial asthma
Periarteritis nodosa
Exsanguination
Various nervous diseases

It will be noted that three of these conditions are represented in this material selected from 1,000 autopsies by less than 5 examples each. The splenic weight for the bronchial asthma group, for instance, might have been considerably altered if there had been a larger material. A small spleen was not anticipated in this condition, which is known to be associated with the lymphatic constitution. On the other hand, my experience with this group was such as to permit the inclusion of the cases in the arbitrarily selected so-called normal class.

TABLE 1.—*Basic Data on Weights of One Thousand Spleens and Livers Arranged by Disease Groups*

| Disease; Disease Group | Cases | Males | Females | Average Age, Yr. | Weight of Spleen, Gm. | | | Weight of Liver, Gm. | | | Liver-Spleen Ratio | Deviation Ratio | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Extremes | Mean Value | Standard Deviation | Extremes | Mean Value | Standard Deviation | | of Spleen | of Liver |
| Arteriosclerosis | 65 | 32 | 23 | 56.6 | 40- 400 | 190.7 | 101.3 | 900-2,840 | 1,660.5 | 425.2 | 8.70 | 1.08 | 1.00 |
| Tumor of the brain | 27 | 17 | 10 | 41.6 | 60- 330 | 145.9 | 75.3 | 970-2,920 | 1,640.6 | 392.3 | 11.24 | 0.82 | 0.99 |
| Traumatic death | 21 | 14 | 7 | 39.6 | 80- 510 | 161.9 | 94.7 | 1,050-2,400 | 1,649.8 | 195.0 | 10.19 | 0.91 | 1.00 |
| Postoperative death without significant primary disease | 22 | 12 | 10 | 53.3 | 60- 330 | 180.0 | 71.9 | 1,200-2,800 | 1,712.3 | 353.0 | 9.51 | 1.01 | 1.04 |
| Acute alcoholism | 1 | 1 | .. | 20.0 | ..... | 260.0 | ..... | ..... | 2,650.0 | ..... | 10.20 | 1.47 | 1.61 |
| Thyroid diseases | 10 | 2 | 8 | 46.4 | 50- 385 | 175.5 | 97.1 | 1,000 1,850 | 1,416.0 | 282.4 | 8.07 | 0.99 | 0.86 |
| Periarteritis nodosa | 3 | 3 | .. | 53.0 | 120- 220 | 156.6 | 45.0 | 1,600-1,650 | 1,626.7 | 20.6 | 10.39 | 0.88 | 0.99 |
| Bronchial asthma | 3 | 3 | .. | 38.3 | 110- 140 | 126.7 | 12.5 | 1,600-1,850 | 1,716.7 | 102.7 | 13.55 | 0.71 | 1.04 |
| Exsanguination | 2 | 2 | .. | 50.5 | 50- 140 | 95.0 | 45.0 | 1,200-1,600 | 1,400.0 | 200.0 | 14.74 | 0.54 | 0.85 |
| Diabetes mellitus | 7 | 5 | 2 | 54.3 | 100- 310 | 227.1 | 67.9 | 1,050-2,230 | 1,758.6 | 383.4 | 7.74 | 1.28 | 1.06 |
| Toxemia of pregnancy | 3 | .. | 3 | 33.7 | 210- 270 | 233.3 | 24.9 | 1,350-2,000 | 1,600.0 | 285.8 | 6.86 | 1.32 | 0.97 |
| Various skin diseases | 4 | 3 | 1 | 41.7 | 90- 320 | 220.0 | 104.6 | 1,110-2,720 | 2,046.2 | 587.7 | 9.30 | 1.24 | 1.24 |
| Various nervous diseases | 6 | 3 | 3 | 41.8 | 85- 200 | 149.2 | 33.7 | 1,050-1,980 | 1,427.5 | 286.8 | 9.57 | 0.84 | 0.86 |
| Poisoning | 2 | 2 | .. | 39.0 | 160- 230 | 195.0 | 35.0 | 1,325-1,540 | 1,432.5 | 107.5 | 7.35 | 1.10 | 0.87 |
| Addison's disease (nontuberculous) | 1 | .. | 1 | 29.0 | ..... | 240.0 | ..... | ..... | 1,310.0 | ..... | 5.46 | 1.35 | 0.79 |
| 1. Diseases without anticipated enlargement of spleen | 177 | 109 | 68 | 48.6 | 40- 510 | 177.5 | 90.0 | 900-2,920 | 1,650.9 | 348.3 | 9.30 | 1.00 | 1.00 |
| Carcinoma | 173 | 123 | 50 | 55.6 | 40- 710 | 187.1 | 101.7 | 640-4,350 | 1,891.7 | 661.7 | 10.11 | 1.05 | 1.15 |
| Sarcoma | 10 | 7 | 3 | 34.7 | 80- 400 | 173.0 | 89.7 | 990-2,400 | 1,586.0 | 397.3 | 9.17 | 0.98 | 0.96 |
| 2. Malignant neoplasms without metastases to the spleen | 183 | 130 | 53 | 54.5 | 40- 710 | 186.4 | 101.1 | 640-4,350 | 1,874.5 | 654.0 | 10.06 | 1.05 | 1.14 |
| Lobar pneumonia | 15 | 8 | 7 | 47.7 | 50- 400 | 196.0 | 327.2 | 1,200-2,100 | 1,735.0 | 319.4 | 8.85 | 1.12 | 1.05 |
| Lobular pneumonia | 18 | 15 | 3 | 52.9 | 75- 430 | 212.2 | 87.0 | 1,000-2,490 | 1,932.8 | 415.6 | 9.12 | 1.20 | 1.17 |
| Peritonitis | 30 | 18 | 12 | 42.3 | 85- 460 | 216.1 | 103.5 | 1,130-4,000 | 1,957.3 | 544.1 | 9.06 | 1.23 | 1.19 |
| Acute and subacute endocarditis and other septic conditions | 85 | 52 | 33 | 36.7 | 20-1,150 | 318.2 | 117.9 | 1,100-4,150 | 2,069.6 | 525.1 | 6.50 | 1.79 | 1.25 |
| Typhoid fever | 7 | 6 | 1 | 30.0 | 185- 510 | 327.1 | 100.0 | 1,650-2,840 | 2,118.3 | 381.7 | 6.48 | 1.84 | 1.28 |
| Acute infectious and purulent conditions | 33 | 22 | 11 | 39.3 | 75- 660 | 228.0 | 131.7 | 1,180-2,860 | 1,905.6 | 412.7 | 8.36 | 1.28 | 1.15 |
| 3. Acute infections | 188 | 121 | 67 | 40.2 | 20-1,150 | 266.5 | 154.2 | 1,000-4,150 | 1,985.5 | 492.0 | 7.52 | 1.39 | 1.20 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Prostatism, ascending urinary infection | 26 | 21 | 5 | 59.3 | 70- 420 | 180.2 | 84.5 | 1,200-2,710 | 1,765.6 | 253.3 | 9.80 | 1.02 | 1.07 |
| Syphilis | 93 | 74 | 19 | 48.4 | 60-1,220 | 237.5 | 160.4 | 890-3,050 | 1,731.4 | 440.7 | 7.29 | 1.34 | 1.05 |
| Tuberculosis | 61 | 30 | 31 | 32.4 | 30- 600 | 209.2 | 116.0 | 1,080-2,720 | 1,690.7 | 385.5 | 8.08 | 1.18 | 1.02 |
| Chronic infections and inflammations | 47 | 30 | 17 | 37.2 | 80- 570 | 194.0 | 98.8 | 930-2,980 | 1,784.9 | 500.8 | 9.20 | 1.09 | 1.08 |
| Actinomycosis | 9 | 6 | 3 | 28.6 | 110- 575 | 309.0 | 144.9 | 1,230-3,000 | 1,941.6 | 553.6 | 6.28 | 1.74 | 1.18 |
| 4. Chronic infections | 236 | 161 | 75 | 42.5 | 30-1,220 | 217.9 | 133.8 | 890-3,050 | 1,743.3 | 346.3 | 8.00 | 1.23 | 1.06 |
| Lymphosarcoma | 17 | 12 | 5 | 44.2 | 50-1,450 | 470.3 | 386.2 | 1,200-5,350 | 2,165.9 | 892.4 | 4.60 | 2.65 | 1.31 |
| Aleukemic lymphoblastoma | 9 | 9 | .. | 52.0 | 130- 920 | 465.6 | 227.2 | 1,500-3,450 | 2,179.4 | 548.7 | 4.68 | 2.62 | 1.33 |
| Lymphatic leukemia | 20 | 15 | 5 | 44.2 | 170-1,330 | 705.8 | 359.7 | 1,830-4,070 | 2,494.7 | 580.6 | 3.54 | 4.00 | 1.51 |
| Myelogenous leukemia | 18 | 12 | 6 | 40.2 | 230-6,400 | 1,635.8 | 1,563.9 | 1,410-4,070 | 2,617.0 | 637.7 | 1.60 | 9.23 | 1.59 |
| Hodgkin's disease | 17 | 11 | 6 | 31.2 | 50-1,850 | 471.5 | 413.7 | 1,300-3,050 | 1,892.0 | 565.3 | 4,01 | 2.66 | 1.15 |
| Multiple myeloma | 4 | 4 | .. | 52.0 | 190- 225 | 213.8 | 13.9 | 1,730-2,510 | 2,013.3 | 352.4 | 9.42 | 1.20 | 1.20 |
| Mycosis fungoides | 3 | 3 | .. | 49.3 | 140- 500 | 308.3 | 148.8 | 1,480-2,420 | 1,861.7 | 395.7 | 6.14 | 1.71 | 1.13 |
| 5. Lymphoblastomas | 88 | 66 | 22 | 42.9 | 50-6,400 | 744.6 | 903.8 | 1,200-5,350 | 2,265.3 | 704.6 | 3.04 | 4.20 | 1.37 |
| Rheumatic heart disease | 19 | 12 | 7 | 35.1 | 100- 385 | 211.5 | 78.8 | 1,130-2,240 | 1,595.6 | 263.2 | 7.56 | 1.19 | 0.97 |
| Uremia, contracted kidneys | 25 | 14 | 11 | 38.9 | 60- 380 | 195.6 | 85.7 | 720-2,630 | 1,680.6 | 369.3 | 8.59 | 1.10 | 1.02 |
| Heart failure | 21 | 15 | 6 | 57.2 | 75- 400 | 208.8 | 88.0 | 1,100-2,860 | 1,645.5 | 380.9 | 7.88 | 1.18 | 1.00 |
| 6. Cardionephropathies | 65 | 41 | 24 | 43.7 | 60- 400 | 204.5 | 85.0 | 720-2,860 | 1,645.2 | 353.7 | 8.04 | 1.15 | 1.00 |
| Agranulocytosis | 3 | 1 | 2 | 27.7 | 220- 470 | 317.0 | 101.1 | 2,080-2,170 | 2,116.7 | 38.6 | 6.68 | 1.79 | 1.28 |
| Pernicious anemia | 24 | 18 | 6 | 49.5 | 60-1,230 | 325.8 | 228.0 | 880-2,680 | 1,962.9 | 866.9 | 6.02 | 1.84 | 1.19 |
| Aplastic anemia | 4 | 4 | .. | 37.8 | 180- 370 | 237.5 | 76.9 | 1,650-2,780 | 2,095.0 | 472.9 | 8.82 | 1.34 | 1.27 |
| Polycythemia vera | 2 | 2 | .. | 49.0 | 150- 330 | 240.0 | 90.0 | 1,470-2,000 | 1,735.0 | 265.0 | 7.23 | 1.35 | 1.05 |
| 7. Blood diseases | 33 | 25 | 8 | 46.0 | 60-1,230 | 309.0 | 203.0 | 880-2,780 | 1,979,0 | 379.4 | 6.40 | 1.74 | 1.20 |
| Amyloidosis | 6 | 4 | 2 | 35.2 | 150- 685 | 256.0 | 191.4 | 1,100-3,100 | 1,973.3 | 866.9 | 7.71 | 1.44 | 1.20 |
| Cirrhosis of the liver | 16 | 12 | 4 | 49.4 | 120- 760 | 488.8 | 208.5 | 720-2,630 | 1,536.4 | 515.2 | 3.14 | 2.75 | 0.93 |
| Banti's disease | 1 | 1 | .. | 48.0 | ..... | 2,220.0 | ..... | ..... | 2,375.0 | ..... | 1.07 | 12.51 | 1.44 |
| Splenomegaly of unknown etiology | 1 | 1 | .. | 41.0 | ..... | 1,536.0 | ..... | ..... | 1,000.0 | ..... | 0.65 | 8.66 | 0.60 |
| 8. Splenomegalies | 24 | 18 | 6 | 45.4 | 120-2,220 | 547.1 | 432.9 | 710-3.100 | 1,658.3 | 660.3 | 3.03 | 3.08 | 1.00 |
| 9. Neoplasms metastatic in spleen | 6 | 4 | 2 | 35.0 | 160- 450 | 295.0 | 109.5 | 1,275-8,960 | 3,288.3 | 2,591,2 | 11.15 | 1.66 | 1.99 |

In the groupings which immediately follow there are other instances in which less than 5 units occur in a class. These may be identified by reference to table 1.

*Normal Size.*—In the following conditions the spleen is, on the average, of normal size (between 90 and 110 per cent of the normal weight, i. e., from 160 to 195.2 Gm.):

- Arteriosclerosis
- Traumatic death
- Postoperative death
- Thyroid diseases
- Poisoning
- Carcinoma
- Sarcoma
- Ascending urinary infection
- Chronic infection and inflammation

*Moderately Large Size.*—With the following diseases moderate enlargement of the spleen is found (from 110 per cent of the normal weight up to 400 Gm.):

- Acute alcoholism
- Diabetes mellitus
- Toxemia of pregnancy
- Various skin diseases
- Tuberculosis
- Actinomycosis
- Multiple myeloma
- Mycosis fungoides
- Addison's disease (nontuberculous)
- Lobar pneumonia
- Lobular pneumonia
- Peritonitis
- Septic conditions
- Typhoid fever
- Acute infectious diseases
- Syphilis
- Rheumatic heart disease
- Uremia, contracted kidneys
- Heart failure
- Agranulocytosis
- Pernicious anemia
- Aplastic anemia
- Polycythemia
- Amyloidosis
- Neoplasms metastatic in spleen

*Extraordinary Size.*—The following diseases are associated with marked enlargement of the spleen (above 400 Gm.):

- Lymphosarcoma
- Aleukemic lymphoblastoma
- Lymphatic leukemia
- Myelogenous leukemia
- Hodgkin's disease
- Cirrhosis of the liver
- Banti's disease
- Splenomegaly of unknown etiology (1 case)

Spleens weighing above 1,000 Gm. were found in individual patients having the following diseases:

- Septic conditions
- Lymphosarcoma
- Lymphatic leukemia
- Myelogenous leukemia
- Hodgkin's disease
- Syphilis
- Pernicious anemia
- Banti's disease
- Splenomegaly of unknown etiology

Regarding the nine disease groups, the preceding lists show that the diseases of group 1 are found associated with small, normal and moderately enlarged spleens in equal distribution, each of the latter categories showing five of the fifteen subgroups. This unanticipated

balance provides further justification for the method by which the basic so-called normal splenic weight was obtained. The admission of deaths from exsanguination, in which a spleen somewhat smaller than normal is anticipated, has been compensated for, if not overcompensated for, by the admission of deaths from toxemia of pregnancy, acute alcoholism and other conditions in which terminal passive congestion may be an important element. In group 2, in spite of considerable individual variation, the average weight of the spleens in both the carcinoma and the sarcoma subgroup is substantially normal. Groups 3, 6, 7 and 9 show, uniformly, moderate splenic enlargement; while group 4 has in part normal, and in part moderately enlarged, spleens. Marked splenic enlargement is found only in groups 5 and 8.

### DISEASES ASSOCIATED WITH DIFFERENT SIZES OF THE LIVER

*Small Size.*—The following diseases are, on the average, associated with small size of the liver (below 90 per cent of the so-called normal hepatic weight of 1,650.9 Gm., i. e., 1,486 Gm.):

Thyroid diseases
Exsanguination
Various nervous diseases
Addison's disease (nontuberculous)
Poisoning
Splenomegaly of unknown etiology

*Normal Size.*—The following diseases are associated with normal size of the liver (between 90 and 110 per cent of the so-called normal weight, i. e., from 1,486 to 1,816 Gm.):

Arteriosclerosis
Tumor of the brain
Traumatic death
Postoperative death
Periarteritis nodosa
Bronchial asthma
Diabetes mellitus
Toxemia of pregnancy
Sarcoma
Lobar pneumonia
Ascending urinary infection
Syphilis
Tuberculosis
Chronic infection and inflammation
Rheumatic heart disease
Uremia, contracted kidneys
Heart failure
Polycythemia
Cirrhosis of the liver

*Moderately Large Size.*—With the following diseases there is moderate enlargement of the liver (between 110 per cent of the so-called normal hepatic weight and 2,200 Gm.):

Various skin diseases
Carcinoma
Lobular pneumonia
Peritonitis
Septic conditions
Typhoid fever
Acute infectious diseases
Actinomycosis
Lymphosarcoma
Aleukemic lymphoblastoma
Hodgkin's disease
Multiple myeloma
Mycosis fungoides
Agranulocytosis
Pernicious anemia
Aplastic anemia
Amyloidosis
Banti's disease

*Extraordinary Size.*—The following diseases are, on the average, associated with marked enlargement of the liver (over 2,200 Gm.):

- Lymphatic leukemia
- Myelogenous leukemia
- Neoplasms metastatic in spleen
- Banti's disease (1 case)
- Acute alcoholism (1 case)

Livers weighing over 3,000 Gm. were found in individual patients with the following diseases:

- Carcinoma
- Peritonitis
- Septic conditions
- Syphilis
- Actinomycosis
- Lymphosarcoma
- Aleukemic lymphoblastoma
- Lymphatic leukemia
- Myelogenous leukemia
- Hodgkin's disease
- Amyloidosis
- Neoplasms metastatic in spleen

TABLE 2.—*Average Splenic Weights in Both Sexes in Various Disease Groups*

| Disease Group | Cases in Males | Splenic Weight, Gm. | Cases in Females | Splenic Weight, Gm. | Female Splenic Weight / Male Splenic Weight |
|---|---|---|---|---|---|
| So-called normal | 109 | 185.7 | 68 | 164.2 | 0.88 |
| Malignant neoplasm | 130 | 184.9 | 53 | 189.8 | 1.02 |
| Acute infection | 121 | 265.7 | 67 | 261.2 | 0.98 |
| Chronic infection | 161 | 220.6 | 75 | 212.1 | 0.96 |
| Lymphoblastoma | 56 | 858.7 | 32 | 545.0 | 0.63 |
| Cardionephropathy | 42 | 211.0 | 23 | 203.2 | 0.96 |

TABLE 3.—*Average Hepatic Weights in Both Sexes in Various Disease Groups*

| Disease Group | Cases in Males | Hepatic Weight, Gm. | Cases in Females | Hepatic Weight, Gm. | Female Hepatic Weight / Male Hepatic Weight |
|---|---|---|---|---|---|
| So-called normal | 109 | 1,754.7 | 67 | 1,482.0 | 0.84 |
| Malignant neoplasm | 125 | 1,949.9 | 53 | 1,697.6 | 0.87 |
| Acute infection | 120 | 2,039.3 | 66 | 1,887.9 | 0.92 |
| Chronic infection | 160 | 1,777.2 | 75 | 1,671.1 | 0.94 |
| Lymphoblastoma | 53 | 2,525.2 | 31 | 1,821.0 | 0.72 |
| Cardionephropathy | 42 | 1,700.0 | 22 | 1,531.0 | 0.90 |

It will be noted that hepatic weight shows less uniformity of relationship within each of the nine major disease groups than does splenic weight. Only in group 5, the lymphoblastomatous diseases, is there a fairly constant moderate to marked enlargement of the liver.

### SPLENIC WEIGHT AND SEX

As a rule, the spleens of females are smaller than those of males, as shown in table 2. The corresponding hepatic weights are given in table 3.

If the so-called normal group is still considered such for purposes of comparison between the sexes, tables 2 and 3 indicate that the spleen of the female weighs 88 per cent of that of the corresponding male,

and the liver of the female, 84 per cent of that of the male. When attention is turned to the disease groups, however, sufficient variability is noted to indicate that other factors are affecting these ratios. The variability is especially marked in splenic weights, while one finds a relative constancy of the female-male ratio in the hepatic weights, the values ranging around 0.9. The lymphoblastomas form an exception from this constancy, for in this group the ratio for the hepatic weights is but 0.72. There is the same deviation in splenic weights but to an even more marked degree. No explanation for this failure of the spleen and liver of the female to increase in size in the lymphoblastomatous diseases in the same proportion as those of the male can be given (save on the basis of the differences in stature between the two sexes). The difference between the average ages of the patient in the two sex groups is not sufficiently great to be of significance. The average age of the females is 38.73 years, and that of the males is 43.36 years.

Another marked deviation from a certain constancy in the female-male ratio of splenic and hepatic weights is shown by the splenic weight in malignant neoplastic conditions. This is the only group in which the spleens of females are larger (1.02) than those of males. This finding may be explained by the following facts:

1. Uterine carcinoma constituted a large percentage of the tumors in the 53 females represented in the group of malignant neoplasms. This type of neoplasm is very likely to cause secondary infection, thus producing moderate enlargement of the spleen of the female.

2. The most common malignant neoplasm in males is carcinoma of the gastro-intestinal tract, and in many cases it causes starvation atrophy of the organs, thus lowering the average weight of the spleen of the male.

3. The average age of the males represented in the group with malignant neoplasms was 57 years; that of females, 48.9 years. The difference is sufficiently large to determine the presence of moderate atrophy due to advancing years. The fact that in malignant neoplastic conditions the liver is not influenced by these circumstances, as shown in table 3, may indicate that the first of the three reasons given is the most important.

## RELATIONSHIP BETWEEN WEIGHT OF SPLEEN AND WEIGHT OF LIVER

In figure 1 splenic and hepatic weights are brought graphically into relationship. The abscissas represent average splenic weights at intervals of 50 Gm., and the ordinates, average hepatic weights at intervals of 100 Gm. The curves are plotted from the data in table 4.

The four curves in figure 1 show a distinct resemblance, indicating a rather constant relationship between splenic weight and hepatic weight. Curves 1 and 3 are in part almost straight lines. One sees a definite rise of the hepatic weight with increasing splenic weight. It is surprising that the same observation can be made even in patients with malignant neoplasms, although in these patients the enlargement of the liver is due chiefly to the more or less incidental presence of metastases, and not to a possible functional relationship between the liver and the spleen.

This observation leads to the suggestion that the spleen and the liver are to a certain degree dependent on one another in respect to

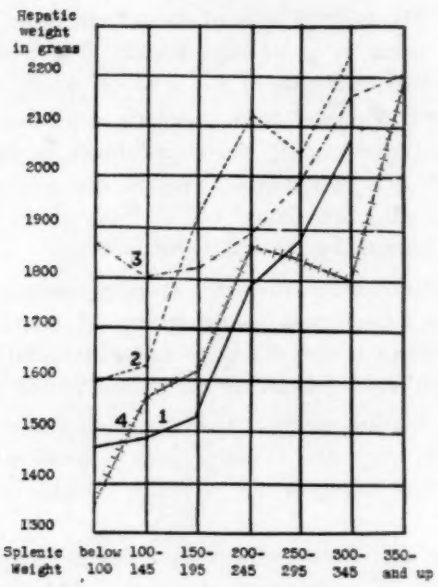


Fig. 1.—Hepatic weights associated with various splenic weights in disease groups 1 to 4, as marked.

TABLE 4.—*Average Hepatic Weights in Successive Splenic Weight Classes for Four Disease Groups*

| Splenic Weight, Gm. | Group 1 | | Group 2 | | Group 3 | | Group 4 | |
|---|---|---|---|---|---|---|---|---|
| | Cases | Hepatic Weight, Gm. | Cases | Hepatic Weight, Gm. | Cases | Hepatic Weight, Gm. | Cases | Hepatic Weight, Gm. |
| Below 100 | 27 | 1,470.2 | 24 | 1,504.8 | 11 | 1 865.0 | 17 | 1,364.7 |
| 100-145 | 53 | 1,486.0 | 44 | 1,625.5 | 30 | 1,802.7 | 48 | 1,570.3 |
| 150-195 | 32 | 1,528.8 | 47 | 1,927.3 | 25 | 1,825.8 | 58 | 1,619.6 |
| 200-245 | 22 | 1,791.0 | 29 | 2,119.1 | 34 | 1,892.2 | 49 | 1,865.5 |
| 250-295 | 19 | 1,870.8 | 14 | 2,042.8 | 17 | 1,989.4 | 22 | 1,837.0 |
| 300-345 | 22 | 2,078.0 | 20 | 2,243.0 | 27 | 2,162.4 | 16 | 1,799.4 |
| 350 and up | .. | ..... | .. | ..... | 42 | 2,203.0 | 25 | 2,187.6 |

size. It is not necessarily the primary disease which causes enlargement of both the spleen and the liver; but, if one organ is primarily affected, the other also enlarges through this dependent relationship. Likewise, both organs are dependent on related circulatory phenomena for a part of their variation in size, as in cardiac insufficiency. Since the curve for the substantially normal disease group 1 is almost a straight line, it follows, also, that a person who is intrinsically endowed with a large liver has likewise a large spleen, and vice versa.

On the assumption that a significant relationship exists between hepatic and splenic weights, the ratio between these weights (liver weight/splenic weight) was computed for each disease and disease group. Like the deviation ratios of the spleen and liver for diseases, this ratio does not necessarily require a large material, as it may be computed for an individual case. The ratio 9.3 of disease group 1, shown in table 1, was considered to be normal. Increase of this ratio may mean either increase of the numerator or decrease of the denominator, and decrease of the ratio may be taken conversely. Table 1 shows that decrease in the size of the spleen and of the liver plays only a minor rôle in the arrangement of this material. The deviation ratios of splenic and hepatic weights are never below 1 in disease groups and only occasionally slightly below 1 in individual diseases. Therefore, an increase of the liver-spleen ratio means practically an enlargement of the liver disproportionate to that of the spleen; decrease, enlargement of the spleen disproportionate to that of the liver. The ratio 3.04 in the lymphoblastoma group illustrates the latter point well. In the presence of malignant neoplasms the ratio is higher than normal, but not so high as might have been expected from the frequency of massive hepatic metastases. This is probably due to the fact that two factors having opposite influences on the weight of the liver are effective in this instance, namely, metastases and marantic atrophy. If this is the correct explanation, it is evident that the former factor is prevalent over the latter in their joint effect on the size of the liver, thus causing a slight increase of the ratio.

Table 5 shows that the liver-spleen ratio for females is smaller than that for males, and apparently to a rather constant degree in every group. Only in the group of malignant neoplasms does the absolute difference between male and female liver-spleen ratios deviate markedly from the general difference. Possible reasons for this have been mentioned in discussing the relationship between sex and splenic weight. When the high level of the liver-spleen ratio in both sexes in group 2 is taken into consideration by computing $\frac{\text{Female Liver-Spleen Ratio}}{\text{Male Liver-Spleen Ratio}}$, it is found that the difference exhibited by group 2 is more apparent than real, for all of the quotients fall within a relatively narrow zone.

SPLENIC WEIGHT AND AGE

Table 6 shows the variations in splenic weight in various decades of life, the figures being obtained for disease groups 1 to 4. These data are shown graphically in figure 2.

The four curves are irregular in appearance and without similarity to each other, except that they show a general tendency toward decrease in splenic size with advancing years. Curve 1, representing the so-called normal spleens, is rather smooth, having a low standard deviation. The expected drop due to senile atrophy is only slight in this group and

TABLE 5.—*Liver-Spleen Ratios in Both Sexes in Six Disease Groups and the Quotients of the Ratios*

| Disease Group | Liver-Spleen Ratio for Males | Liver-Spleen Ratio for Females | Absolute Difference in Ratios | Female Liver-Spleen Ratio / Male Liver-Spleen Ratio |
|---|---|---|---|---|
| 1 | 9.45 | 9.06 | 0.42 | 0.96 |
| 2 | 10.55 | 8.94 | 1.61 | 0.85 |
| 3 | 7.68 | 7.23 | 0.45 | 0.94 |
| 4 | 8.06 | 7.84 | 0.22 | 0.97 |
| 5 | 3.34 | 2.94 | 0.40 | 0.88 |
| 6 | 8.05 | 7.50 | 0.45 | 0.93 |

TABLE 6.—*Splenic Weights in Various Life Decades in Disease Groups 1 to 4*

| Decade of Life | Group 1 Cases | Group 1 Splenic Weight, Gm. | Group 2 Cases | Group 2 Splenic Weight, Gm. | Group 3 Cases | Group 3 Splenic Weight, Gm. | Group 4 Cases | Group 4 Splenic Weight, Gm. |
|---|---|---|---|---|---|---|---|---|
| Under 20* | .. | ..... | | | 26 | 306.7 | 27 | 180.4 |
| 20-29 | 17 | 201.8 | 24 | 227.6 | 37 | 314.5 | 35 | 238.6 |
| 30-39 | 28 | 187.9 | | | 35 | 246.0 | 42 | 248.1 |
| 40-49 | 32 | 192.0 | 36 | 181.8 | 29 | 303.3 | 47 | 240.5 |
| 50-59 | 51 | 167.3 | 55 | 174.6 | 32 | 232.5 | 42 | 197.6 |
| 60-69 | 29 | 158.5 | 45 | 195.0 | 29 | 191.9 | 31 | 184.7 |
| 70 and up | 19 | 176.8 | 23 | 160.4 | | | 12 | 191.1 |

* Only persons of adult stature were included in this material.

in group 2. As to group 1, this observation may be due to the limited number of persons (19) in the highest age group, and as to group 2, it may possibly be explained by the fact that this group is a priori composed of persons who, because of the cachexia due to tumor, present atrophic changes that mask those of senility and that appear at earlier years of life than do changes which are due to senility alone. Disease groups 3 and 4 show a distinct drop after the fifth decade.

Senile atrophy plays a surprisingly minor rôle so far as this material shows. The decrease in splenic weight, frequently very marked in individual cases, disappears in a larger material. Table 1 shows that the

deviation ratio of the spleen is slightly below 1 in some of the diseases but never in disease groups. This purely mathematical phenomenon does not exclude, of course, the anatomic significance of reduced splenic weight. It demonstrates, perhaps, that intrinsic death (death from old age alone) is exceedingly rare.

The spleens and livers of all persons of 70 years of age and over were selected from disease group 1 and the spleens also from group 2, and the mean values of both series were obtained. The average weight of the livers (17) was found to be 1,521 Gm.; that of the spleens (39), 168.6 Gm., values which are 92.2 and 95 per cent of the so-called normal weights for all ages, respectively. The liver-spleen ratio of the

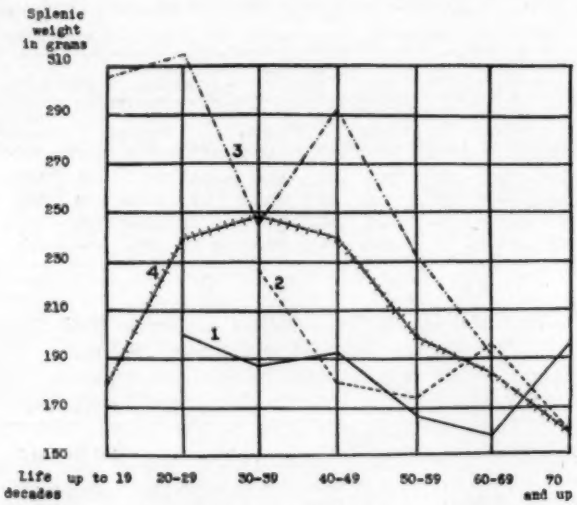


Fig. 2.—Splenic weights associated with various decades of life in disease groups 1 to 4, as marked.

older group is 9.03, indicating an almost parallel reduction in size of the liver and spleen in old age, since the so-called normal ratio is 9.3. This point was investigated further by determining the average splenic weight for 32 persons in these groups below 70 years of age (183.6 Gm.) and the average hepatic weight in 159 persons also below 70 years of age (1,664.7 Gm.). For these groups the liver-spleen ratio is 9.07. The essential identity of these ratios further supports the conclusion that there is parallel reduction in these organs as age advances. The average age of all persons with spleens weighing below 100 Gm. was found to be 51.45 years, which lies above the average age of each disease group with the exception of group 2 (malignant neoplasms).

### SPLENIC WEIGHT AND STATURE

In order to determine the relationship between stature and splenic weight in various disease groups, the present material was divided into three classes for each sex, consisting of short persons, persons of medium height and tall persons. For males the limits of these classes were established as (1) below 170 cm. in body length, (2) between 170 and 179 cm., and (3) 180 cm. and up, and for females, as (1) below 160 cm. in body length, (2) between 160 and 169 cm. and (3) 170 cm. and up.

TABLE 7.—*Splenic Weights in Three Stature Classes in Both Sexes in Disease Groups 1 to 4*

| | Male Sex | | | | | | Female Sex | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Stature Below 170 Cm. | | 170-179 Cm. | | 180 Cm. and Up | | Below 160 Cm. | | 160-169 Cm. | | 170 Cm. and Up | |
| Disease Group | Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. |
| 1..... | 25 | 175.8 | 56 | 182.5 | 25 | 212.8 | 16 | 127.8 | 45 | 177.1 | 6 | ..... |
| 2..... | 47 | 172.9 | 62 | 182.8 | 20 | 215.5 | 17 | 172.6 | 22 | 195 | 13 | 212.7 |
| 3..... | 30 | 268.7 | 61 | 272.9 | 26 | 270.8 | 15 | 195.7 | 42 | 250.6 | 8 | ..... |
| 4..... | 45 | 203.3 | 82 | 229 | 32 | 244.5 | 22 | 158.6 | 44 | 222 | 8 | ..... |

TABLE 8.—*Splenic Weights in Three Stature Classes in Both Sexes, the Data for Disease Groups 1 to 4 Being Combined*

| Male Sex | | | | | | Female Sex | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Stature Below 170 Cm. | | 170-179 Cm. | | 180 Cm. and Up | | Below 160 Cm. | | 160-169 Cm. | | 170 Cm. and Up | |
| Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. |
| 147 | 202.3 | 261 | 218.3 | 103 | 239.3 | 70 | 162.9 | 153 | 212.8 | 35 | 270.9 |

For the first four disease groups the average splenic weight was determined in each of the resulting twenty-four categories. When less than 10 cases were left in a subgroup by this subdivision of the material, the resulting mean splenic weight was ignored.

Tables 7 and 8 show a definite increase in splenic weight in taller persons. This increase is especially marked in males (a considerably larger material). In spite of the extensive subdivision of the material, table 7 includes but a single exception to the general trend. This close relationship between splenic size and stature suggests that the smaller size of the spleen in females is primarily a statural, and only secondarily a sexual, characteristic.

## SPLENIC WEIGHT AND BODY TYPE

In order to test a possible relationship between splenic size and constitutional type, the individual cases of the four major disease groups were divided into three classes according to the three fundamental constitutional types: eumorphic, brachymorphic and dolichomorphic. It is obvious that this classification lacks accuracy, because the types as given in the protocols were based on the prosectors' subjective impressions rather than on quantitative anthropometry. Since in part such terms as "obese," "slender" and "gouty arthritic" were used in the protocols, some subjects had to be classified by using such terms in connection with the data on body length and the accompanying photographs of the patients. Those determined to be of a dysplastic constitutional type were excluded as unclassifiable. The average splenic weight was obtained in each of these groups and is presented in table 9.

TABLE 9.—*Splenic Weights in Three Different Body Types in Disease Groups 1 to 4*

| Disease Group | Eumorphic | | Dolichomorphic | | Brachymorphic | |
|---|---|---|---|---|---|---|
| | Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. | Cases | Splenic Weight, Gm. |
| 1 | 40 | 184.9 | 78 | 182.3 | 41 | 171.3 |
| 2 | 22 | 255 | 106 | 167.5 | 30 | 178.8 |
| 3 | 25 | 282.2 | 89 | 258.5 | 29 | 259.3 |
| 4 | 40 | 243.4 | 125 | 256.5 | 25 | 242.4 |

The weights in table 9 show but little uniformity of trend except for the fact that in all the groups the eumorphic persons have the largest spleens. The figures on splenic weight in dolichomorphic and brachymorphic persons appear entirely irregular in arrangement in that the dolichomorphic ones have the heavier spleens in groups 1 and 4 and the brachymorphic ones in groups 2 and 3. The larger size of the spleen in the eumorphic person is perhaps explained largely by correlation with the effect of stature, as discussed in the preceding section. Brachymorphic persons constitute in general a shorter group, while dolichomorphic persons as a group are not significantly taller than the eumorphic type. They may even be shorter if among them are included a large number of microsplanchnic persons. Thus the feeble indication of a trend in splenic size in respect to constitutional type, so far as the problem can be approached by this material, can be resolved into a statural effect.

## SUMMARY

From autopsy material 1,000 cases were selected, classified into nine disease groups, and the extremes, means and standard deviations for the weights of the spleens and livers were obtained. Likewise, the ratio

of hepatic weight to splenic weight was computed for each disease and for each disease group.

Since there is no practical method for determining the absolute norm of splenic weight, the norm was approximated by computing the mean weight in 177 cases in which the demonstrated disease conditions were not such as to create an expectancy of increase in the size of the spleen. While this was not an ideal procedure, it proved to be the only practical method for establishing a basis of comparison. The approximate norm for hepatic weight was similarly established.

Ratios, designated "deviation ratios," were computed between the observed mean weight of the spleen for each disease or disease group and the so-called normal weight. Similar deviation ratios were obtained for the liver.

The material was subdivided according to sex, age, stature and constitutional type, and the splenic and hepatic weights, in relationship to certain disease groups, were compared for each of these attributes.

The principal conclusions derived from this investigation are as follows:

1. The mean weight of the spleen in the so-called normal group (all ages and both sexes) is $177.5 \pm 4.6$ Gm.; that of the liver, $1{,}650.9 \pm 17.7$ Gm.
2. With the mean splenic weight for the so-called normal group considered as 1, the corresponding weight ratios for the disease groups are: malignant neoplasms, 1.05; acute infections, 1.39; chronic infections, 1.23; lymphoblastomas, 4.2; cardionephropathies, 1.15; blood diseases, 1.74; splenomegalies, 3.08, and neoplastic diseases with splenic metastases, 1.66.
3. The spleens and livers of females are smaller than those of males of the same ages and of the same disease groups. Only in the group of malignant neoplasms does this relationship differ.
4. The ratio between hepatic weight and splenic weight is as 9.3 to 1 in the so-called normal group. In the disease groups this ratio varies. The liver-spleen ratio in females is smaller than the corresponding ratio in males to a fairly constant degree in each disease group. There is evidence of marked dependence between these organs in respect to size.
5. While there is shown a fairly constant decrease in the size of the spleen and liver with advancing years, senile atrophy plays a less important rôle than was expected in the material investigated.
6. Splenic weight increases with increasing stature.
7. Eumorphic persons have larger spleens than those who are dolichomorphic or brachymorphic. This may be due largely to a statural effect inherent in this grouping.

# Case Reports

## ACTINOMYCOSIS OF THE TUBES AND OVARIES

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Actinomycosis of the internal female genitalia is usually considered a rare disease, but Graves [1] and other authors have stated that it is considerably more common than supposed. Cornell [2] reviewed the literature on seventy-one cases, added a report on one of his own and mentioned another case, a report of which was indexed after his article was submitted for publication. Since then, five additional cases have been reported, two by Counseller and Hoerner [3] and one each by Junghans,[4] Gardiner and Welsh [5] and Hüssy,[6] bringing the total to seventy-eight cases.

The disease is generally considered to be secondary to actinomycosis of the gastro-intestinal tract, especially of the cecum and appendix. Graves stated that it is probably never primary in the tubes or ovaries. The genital tract itself, however, has been deemed the route of entry in some cases, including that of Junghans and that of Gardiner and Welsh. The disease presents no typical clinical picture and usually resembles other chronic inflammatory or even malignant conditions of the pelvis. The diagnosis is usually established by histologic examination of tissue, but a few cases have been diagnosed by examination of the pus obtained by colpotomy. The relative infrequency of the latter method of diagnosis is apparently due to the fact that the pus frequently does not present the typical radiate filamentous organisms but only fragments of hyphae resembling bacilli. Davis [7] pointed out that many infections of this type are probably missed because of this feature. Furthermore, these organisms are frequently extremely difficult to culture, especially when associated with other pyogenic organisms. The generally accepted treatment in these cases is complete surgical removal of involved tissue, administration of potassium iodide by mouth and roentgen or radium therapy. Cornell classified eleven of the

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seventy-one cases which he reviewed as attended with possible cures, and eight, with improvement. The outcome was doubtful in seven, and in forty-five the patient died.

REPORT OF CASE

A white housewife 30 years old was admitted to New York City Hospital to the gynecological service of Dr. E. P. Colie, May 25, 1934, because of chill, vomiting and severe pain in the right lower quadrant of the abdomen of about twelve hours' duration. She had always been well up to three months previously, when she

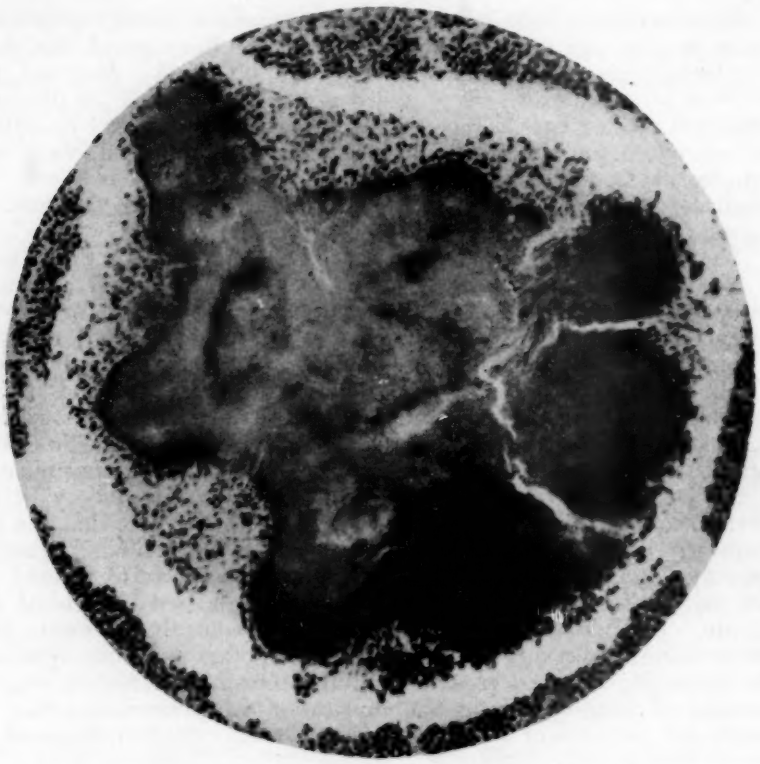

Fig. 1.—A low power photomicrograph of an actinomycotic abscess.

suffered severe pain in this region of the abdomen lasting a few days. A vaginal discharge had been present since the onset of her illness. A month after the first attack of pain she had a recurrence lasting one day. The menstrual history was normal, and she had given birth to two normal full-term infants. She said that she had never had venereal disease or miscarriages.

She appeared chronically ill. There was a bulging fluctuant tender mass filling the pelvis and culdesac. The uterus was not felt; the cervix was firm, lacerated and fixed anteriorly. A vaginal discharge was present but was not examined bacteriologically. The lower part of the abdomen was tender to pressure. Otherwise the physical examination revealed nothing of importance except poor oral hygiene. There were leukocytosis, moderately severe secondary anemia, a rapid

sedimentation rate and a septic temperature. The Wassermann reaction of the blood was negative. Urinalysis revealed albumin (1+) and a few granular casts and pus cells. An x-ray picture of the chest revealed only increased markings at the roots of the lungs. On May 28, three days after admission, colpotomy was performed and a quart of foul-smelling greenish pus obtained. On culture, this gave a mixed growth with no gonococci. On June 27 colpotomy gave a smaller amount of pus, which was negative on culture. After this, reexamination revealed an orange-sized cystic mass in the left adnexal region. The patient improved and was discharged June 22, 1934. She was advised to return later for further treat-

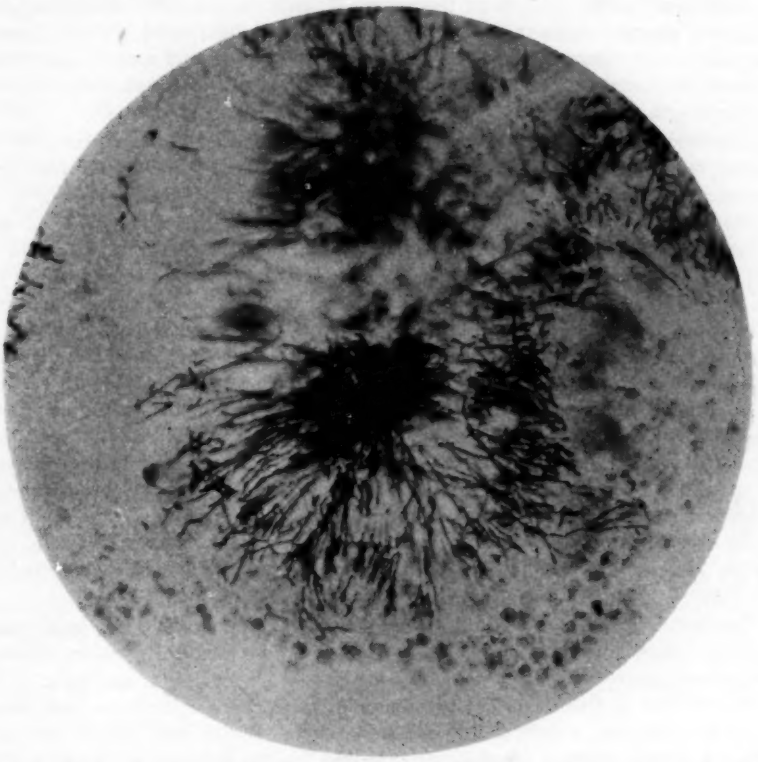

Fig. 2.—A high power photomicrograph of an actinomycotic colony stained by Gram's technic, showing the filamentous character of the colony and the radiate border.

ment. During her first stay in the hospital she received three transfusions and daily administrations of iron and ammonium citrate.

She was readmitted September 27. In addition to the left adnexal mass, a fluctuant mass was felt in the right parametrium. The temperature was again septic. On October 1, colpotomy gave about 4 ounces (118 cc.) of pus, which was not cultured. On November 7, colpotomy was performed again. A direct smear of the pus showed gram-positive cocci and gram-positive filamentous organisms very similar to Actinomyces. Culture showed a green streptococcus and a bacillary

organism not typical of Actinomyces. After the last colpotomy, there was a drop in temperature with steady clinical improvement. On December 10, laparotomy was performed. The findings were those of a chronic adnexal inflammatory disease with extensive adhesions. The uterus was amputated supracervically and removed with both adnexal masses. Four days after the operation, a rather severe infection of the abdominal wound developed, which cleared up in about three weeks with use of surgical solution of chlorinated soda and ultraviolet ray therapy. Culture of material from the wound revealed streptococci and mixed bacilli. The patient was discharged much improved on Jan. 15, 1935. During her second stay in the hospital she received two blood transfusions, daily administrations of iron and ammonium citrate and, from December 27, potassium iodide. After her discharge she was under the care of Dr. M. Rashbaum, who treated her with potassium iodide and roentgen therapy. On Sept. 19, 1936, twenty months after her discharge, she was apparently in good health, with no pelvic masses palpable, and Dr. Rashbaum considered her cured.

*Pathologic Observations.*—The operative specimen consisted of a uterus with an attached adnexal mass and a separate tubo-ovarian mass. The uterus had been amputated supracervically and was entirely normal grossly and histologically.

The distal half of the attached tube was incorporated in a mass about 4.5 cm. in diameter, covered by a thick gray-yellow substance, glistening and smooth in some parts, ragged in others. On section, disorganization was so extreme that the tube and ovary could not be differentiated with certainty. The cut surface presented a fibrotic, variegated appearance; it was flecked irregularly with yellow, gray and orange and showed brown and white necrotic areas. There were several large brown gelatinous bodies with narrow serpentine rims of yellow, as well as several cysts, chiefly peripheral, from 2 to 5 mm. in diameter, containing clear serous fluid. The proximal half of the tube was free and very thick; it had a thick, granular serosa. On section, the wall was dense and firm, and the lumen was dilated by a light gray gelatinous material surrounded by a narrow yellow zone.

The separate tubo-ovarian mass was much larger, measuring 7 by 5 by 4 cm. It was approximately similar to the attached mass except that no free tube was present, and on the cut surface thickened tubal wall could be recognized in some parts.

*Histologic Observations.*—Both adnexae showed numerous large and small abscesses, many of them containing actinomycotic colonies. These colonies appeared granular, their peripheries staining purple (hematoxylin and eosin); the peripheries had a distinct radial arrangement, with nodular agglutination along the borders but only a rare, highly refractile club. The centers stained pink and contained poorly staining interlacing threadlike purple structures. Gram's stain revealed, coursing throughout a pink ground-work, an interlacing mycelial mass, arranged radially on the periphery, conglomerated in the center. The hyphae were moderately coarse with frequent branching at all angles; they often appeared as thin double-walled tubes with marked spirillary courses. Some hyphae were gram positive, others gram negative, and some individual threads showed different reactions in different portions. The hyphae were intricately beaded by small bulbous swellings; the majority were gram positive, but some were gram negative. The occasional peripheral club stained gram negative. In the immediate vicinity of the colonies were many fragments of hyphae lying free in the inflammatory exudate or being engulfed by polymorphonuclears and swollen macrophages. Around the abscesses were thick walls of chronic granulation tissue containing an occasional giant cell and a few fragments of hyphae and merging into the surrounding tissue.

Outside the walls of the abscesses both adnexae showed very extensive disorganization by fibrosis, edema and a very heavy infiltration by lymphocytes, monocytes, many plasma cells, some eosinophils, and polymorphonuclears in variable numbers. In the attached adnexal mass, ovarian tissue but no tube was preserved. The free portion of the tube showed a similar disorganization of the wall; the lumen was filled with pus, and the mucosa was partially destroyed. Many xanthoma cells were present in the preserved mucosa. Lying free in one area of edematous subserosa, not surrounded by cells, were some tiny clumps and scattered groups of organisms similar to the hyphae described previously but much shorter and even cocciform, showing also both gram-positive and gram-negative reactions; some bore a marked resemblance to diphtheroid organisms. The clumps showed a distinct tendency toward radial arrangement. In the separate adnexal mass, individual coils of the tube were preserved, and one of them contained a few scattered gram-positive hyphae just beneath the mucosa. Present in both disorganized adnexae were many tubercle-like structures with a concentric whorl formation, occasionally with early central necrosis, in which bacteria were not demonstrable. No organisms were found in any areas outside those mentioned. On the surfaces of both adnexae were many plaques of fibrinopurulent exudate.

## COMMENT

The clinical course in this case resembled that of inflammatory pelvic disease of the usual type and the condition was regarded as such even after the operative specimen was examined grossly. It was not until the histologic examination was made that the nature of the disease was discovered. In the gross specimens no recognizable "sulfur granules" were found, even when the specimens were reexamined subsequent to the histologic diagnosis. Only once did bacteriologic examination reveal an organism similar to Actinomyces, and this was on direct smear from the pus obtained by colpotomy. Cultures of this pus as well as of material from the other specimens obtained at colpotomy failed to reveal any actinomycotic organisms. After the diagnosis was established, an attempt was made to obtain cultures from the depths of the specimens fixed in solution of formaldehyde U. S. P., but this was unsuccessful.

## SUMMARY

A case of actinomycosis of the tubes and ovaries is presented.

# ACTINOMYCOTIC ABSCESS OF THE BRAIN

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Involvement of the central nervous system by actinomycosis is rare and usually occurs as a hematogenous metastatic lesion from a focus elsewhere in the body or by direct extension from lesions involving the skull and soft parts of the face and throat (Moersch,[1] Orlow,[2] Sanford and Voelker,[3] Werthemann,[4] Smoke,[5] Shapiro,[6] Topley,[7] and others). More rarely, and questioned by some, is the primary involvement of the nervous system as recorded by Bollinger,[8] Buday,[9] Enriguez and Sicard,[10] Russkich and Krylowa.[11] It is with the latter phase in mind that we present a case of cerebral actinomycosis which at first suggested a primary focus in the brain.

## REPORT OF CASE

H. D., aged 20, entered the Cook County Hospital on Jan. 3, 1936. One month previous to his admission a cough had developed, which was followed by pain in the chest. He lost his appetite and vomited almost every time he ate, so that there was considerable loss of weight. About ten days prior to his entrance to the hospital headaches developed, which grew progressively worse and were followed later by stiffness of the neck. The past history was essentially irrelative except for the usual diseases of childhood. He stated that he had had no venereal diseases.

He was a well developed white man who appeared acutely ill. The temperature was 103 F.; the pulse rate, 100; and the respiratory rate, 30. Examination of the chest revealed slight dulness with diminished breath sounds in the left lower lung field. The expansion movements were likewise slightly decreased.

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The pupils were round and equal and reacted well to light and in accommodation. The external ocular movements were intact. There was marked rigidity of the neck with Brudzinski and Kernig signs. Sensory disturbances could not be elicited. Bladder and rectal disturbances were absent. Ophthalmoscopic examination revealed bilateral choking of the disks of 4 diopters.

Spinal puncture showed the spinal fluid to be cloudy and under markedly increased pressure. The Pandy test was positive, and the cell count was 2,440 per cubic millimeter, the polymorphonuclear leukocytes predominating. Smears stained with the methods of Gram and Ziehl-Neelsen failed to demonstrate any organisms. The analyses of the urine and blood gave essentially negative results. The Wassermann reaction of the spinal fluid was negative. The sugar content of the spinal fluid was determined to be 9 mg. and the chloride content 690 mg., per hundred cubic centimeters. A roentgenogram of the chest disclosed an opacity in the left lower lung field, suggestive of pneumonia. There was no evidence of tuberculosis. Repeated cultures and smears of the spinal fluid were negative for tubercle bacilli. The relatively heavy precipitate indicated meningitis other than tuberculous in origin.

Antimeningococcic serum and 500 cc. of a 10 per cent dextrose solution were administered intravenously. The temperature ranged from 99 to 104 F. The patient vomited occasionally and appeared irrational. Generalized twitchings of the body, difficulty in swallowing and involuntary movements developed. The patient died two weeks after his entrance into the hospital and one and one-half months after the onset of the symptoms. Clinically, the condition resembled tuberculous meningitis, but the findings in the spinal fluid suggested purulent meningitis secondary to a pulmonary involvement.

*Necropsy* (Dr. R. H. Jaffé).—The right pleural cavity was free; the left revealed focal fibrous adhesions about the posterior aspect of the left lower pulmonary lobe. The right lung was moderately distended and crepitant. Beneath the pleura of the lower lobe there was a dark red patch, 3 cm. long, which on sectioning was purple-gray and moist. The left lung was crepitant throughout. Beneath the pleura of both lobes, especially the lower, there were confluent dark red patches which on sectioning were purple-brown and moderately moist.

The essential gross pathologic changes were in the brain. The convolutions over the cerebral hemispheres were flattened, and the leptomeninges were slightly thickened. At the base of the brain, in the region of the pons and the cerebellar cistern, the leptomeninges were separated by a light yellow-gray exudate with soft fibrinous flakes. The brain substance was moist and soft. The cortex and the basal ganglions were light purple-gray. In the white matter of the right frontal lobe, extending into the anterior part of the parietal lobe, were two spherical cavities 23 and 20 mm. in diameter. These cavities were filled with thick mucoid material of a light grayish-green color and were lined by a moderately firm, light purple-gray membrane, 2 mm. thick. One of these abscesses was located in the middle third of the frontal lobe; the other was in the lower third; between them was a layer of edematous brain tissue, 3 mm. thick (fig. 1 *A*). The lower cavity had broken through the ependymal lining of the anterior horn into the lateral ventricle (fig. 1 *B*). The ventricles were markedly dilated and filled with purulent material.

Direct smears from the abscess cavities of the brain, taken at the time of the autopsy, revealed pus cells and a moderate number of slender, branched gram-positive filaments with slight clubbing at their ends and containing numerous minute granules (fig. 2 *A*). No other micro-organisms could be detected.

Examination of the middle ears, sinuses and tonsils revealed nothing abnormal.

The lungs were placed in Kaiserling's solution and after fixation were cut in very thin sections. An indurated area, 25 by 35 mm., dark purple-gray and streaked with light yellow-gray lines, was found on the median aspect of the left lower pulmonary lobe, near the base. This area centered on an irregular cavity, 10 by 6 mm. in its greatset diameters (fig. 3). The cavity was connected with a small bronchus, which was lined by a finely granular, dark purple-red membrane. Smears taken from the lining of this cavity revealed filamentous organisms similar to those found in the cerebral cavities. These organisms were also recovered in pure cultures from the abscesses of the brain and from the meninges (fig. 2 *B*).


Fig. 1.—*A*, two localized abscesses in the subcortical white matter of the brain; *B*, one of the abscesses, extending through the roof of the lateral ventricles.

*Anatomic Diagnosis.*—The following conditions were found: Two actinomycotic abscesses of the right frontal lobe with perforation of one into the lateral ventricle; diffuse suppurative leptomeningitis; small cavity with actinomycotic filaments in the left lower pulmonary lobe; parenchymatous degeneration of the myocardium and kidneys; parenchymatous degeneration and fatty changes of the liver; infectious softening of the spleen, and focal fibrous adhesions and subpleural hemorrhages over both lungs.

*Microscopic Examination.*—Brain: The subcortical abscesses in the right frontal region were separated from the cerebral parenchyma by a poorly developed, young connective tissue capsule. The innermost portion of the capsule, adjacent

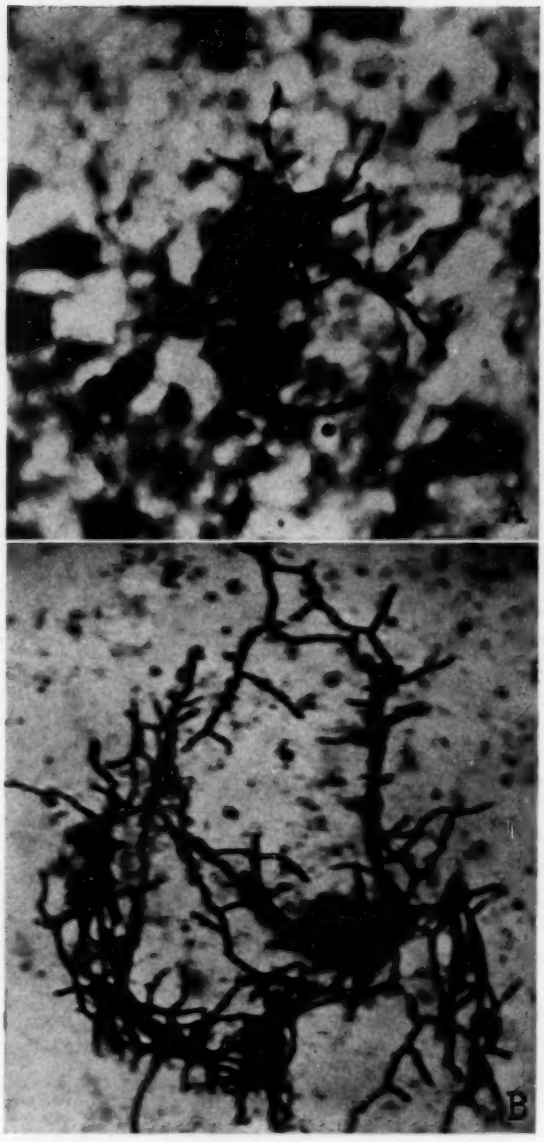



Fig. 2.—*A*, filamentous organisms with slight clubbing at their ends obtained by direct smear from the abscess cavity in the brain. *B*, numerous branched filamentous organisms obtained by smear from an aerobic culture on Harold's medium; oil immersion; methylene blue stain.

to the pus within the cavity, was composed of dense masses of compound granular corpuscles (the contents of which stained with sudan III), degenerated polymorphonuclear leukocytes and a few plasma cells. Sections stained by the Van Gieson method revealed swollen fibrocytes among these cells. The outermost portion of the capsule, bordering the cerebral parenchyma, was formed by denser connective tissue fibers and swollen fibrocytes, which were particularly marked about small blood vessels. In the middle layer of the capsule the predominant features were dilated blood vessels and capillaries surrounded by a loose network of swollen fibrocytes and young connective tissue fibers, histiocytes, plasma cells and polymorphonuclear leukocytes. In some places these infiltrations were marked and

Fig. 3.—Photomicrograph showing an actinomycotic abscess (10 by 6 mm. in greatest diameters) in the lung, lined by vascular granulation tissue; low power magnification; hemalum-eosin stain.

extended throughout the capsule wall. The lumen of the abscess was filled with débris of degenerated polymorphonuclear leukocytes. Gram-Weigert staining of sections of the lining of the abscess cavity and particularly of the innermost layer of the capsule revealed elongated filamentous, thread-shaped gram-positive microorganisms. These showed frequent dichotomous branching and appeared semitransparent. Their protoplasm was beaded, forming round deep-staining granules that varied slightly in size (fig. 4 *A*). Frequently these organisms were collected into small dense foci and appeared like chains of small streptococci enclosed in tubes.

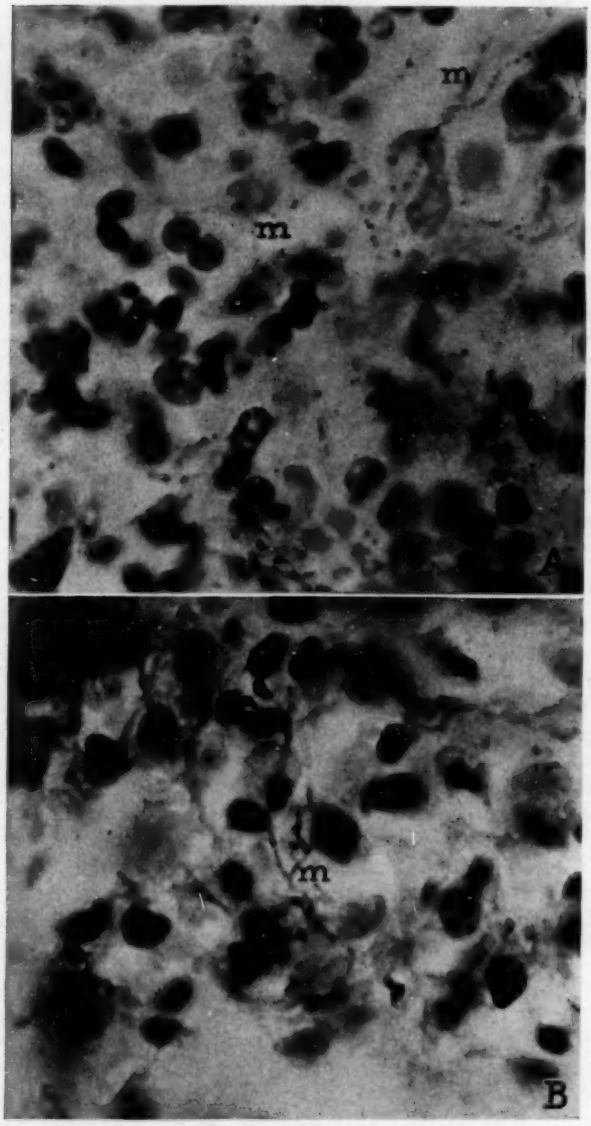



Fig. 4.—*A*, histologic appearance of the wall of one of the abscesses in the brain. The actinomycete is seen as filaments which are totally similar to such structures in the wall of the abscess in the lung, shown in *B*. At *m* is a slender, elongated filamentous organism, the protoplasm of which is beaded, forming round deep-staining granules; oil immersion; Gram-Weigert stain.

At one point the abscess had broken through the roof of the anterior horn of the lateral ventricle. Beneath the ependyma in the region of the abscess were marked perivascular infiltrations. The brain tissue in the vicinity of the abscess appeared loosened, and numerous microgliacytes (rod cells) and cytoplasmic glia cells were present. The blood vessels in this region were congested, showed marked proliferation of their adventitial layer and widening of their Virchow-Robin spaces, which were filled with large numbers of lymphocytes and plasma cells.

The leptomeninges, particularly at the base of the brain, were thickened and densely infiltrated with cells of the type previously mentioned. In sections stained with toluidine blue the intermeningeal exudate revealed numerous branched mycelia. The cellular infiltrations were particularly prominent about the pial blood vessels, infiltrating their walls as well as the perineurial spaces of the nerve roots. The endoneural cells of the nerve roots were swollen. Similar infiltrations were found in the meninges of the spinal cord.

The cyto-architecture of the cerebral cortex was well preserved, but the ganglion cells in the lower cortical layers and in the vicinity of the abscesses showed regressive changes. They were often shrunken and stained poorly; their processes were indistinct, and their cytoplasm was almost completely devoid of Nissl bodies.

The tuft cells of the choroid plexus were swollen, and in some areas the choroid plexus was densely infiltrated with polymorphonuclear leukocytes forming small abscesses.

Lung: The small cavity in the left lower pulmonary lobe was lined by a very vascular granulation tissue, which was composed of lymphocytes, mononuclear cells, plasma cells and a few polymorphonuclear leukocytes (fig. 3). The capillaries were congested, and there were many recent extravasations of blood. In Gram-Weigert stained sections numerous long, slender branched threads were found, the cytoplasm of which was beaded (fig. 4*B*). These threadlike organisms were present within the cavity and extended between the cells of the innermost layer of the granulation tissue. There was an occasional large multinucleated cell which contained segments of these threads. The lining tissue about the cavity was sclerosed and densely infiltrated by round cells, mononuclear cells and plasma cells. The alveoli were obscured, and there were many tubular, glandlike structures, which were lined by cylindric epithelium. At the periphery of the area of induration the lung tissue was slightly emphysematous and congested. The smaller branches of the pulmonary artery showed distinct thickening of their intimal layer.

## COMMENT

Although there have been a number of reports of primary actinomycosis of the central nervous system in the literature (twenty-three cases were mentioned by Friedman, Plaut and Levy [12]), further examination of the necropsy records revealed them to be incomplete and inadequate in most cases. This was due to the inadequate postmortem examination of the middle ears, paranasal sinuses, tonsils and other organs which might have originally harbored these micro-organisms. Likewise Jacoby [13] refers to only three cases which can stand critical analysis.

12. Friedman, E. D.; Plaut, A., and Levy, H. H.: J. Nerve. & Ment. Dis. **83**:569, 1936.

13. Jacoby, F.: Arch. f. klin. Chir. **149**:621, 1928.

The possibility of failure to identify the primary source of infection during necropsy is well illustrated in our case. The finding of actinomycetes in the abscesses of the brain led to an immediate further search for a possible primary source of infection. Examination of the throat, sinuses and middle ears and reexamination of the lungs and abdominal organs failed to disclose an active actinomycotic lesion at the time. Thus, at first the possibility of primary actinomycotic abscesses of the brain was considered. The further history obtained from the family revealed that the patient had sustained a trauma to the head two months prior to the onset of the symptoms.

It was only after fixation in Kaiserling solution that careful sectioning of the lungs into very thin slices disclosed the primary focus of infection in the form of a circumscribed small cavity in the left lower lobe. A similar case has been described by Becker,[14] in which an actinomycotic abscess of the brain was secondary to focal empyema of the chest and to a cherry-sized abscess in the lung.

With such small foci in the lung it can be realized how the examiner may fail at the necropsy to identify the primary lesion even after close scrutiny of the organs. Further difficulty might arise from the presence of small foci elsewhere in the body, particularly in the cervicofacial region, where they might have healed with scar formation after the active stage had led to the formation of a metastatic abscess of the brain.

Wright [15] first suggested that the actinomycotic micro-organism might exist as a harmless inhabitant of the mouth or gastro-intestinal tract, becoming pathogenic only when it gains entrance through some local lesion. Lord [16] and Naeslund [17] both furnished strong support to this view. They isolated the micro-organisms from the teeth and crypts of the tonsils of normal human subjects and produced actinomycotic lesions in the animals inoculated with them.

Actinomycosis may involve the central nervous system, according to Jacoby,[13] in the form of meningitis, an encapsulated abscess or a gelatinous granulation tumor. The meningeal type, in which the infection usually takes place by continuity, is the most frequent. The lesion erodes all structures in its path, as was evidenced in one of the cases which came to necropsy at the Cook County Hospital; in this instance there was a compression of the spinal cord due to an extensive involvement of the vertebral column secondary to a primary focus in the gastro-intestinal tract. The localized abscesses of the brain usually follow a hematogenous spread from the lungs, mouth or gastro-intestinal tract. Invasion along the lymphatics and lymph glands, except for the perineurial spaces in the nervous system, has not been noted.

The histologic features of the abscess wall and of the area of nonsuppurative encephalitis surrounding the abscess in this case are similar to those previously described by us.[18]

14. Becker, H.: Deutsche Ztschr. f. Nervenh. **134**:36, 1934.

15. Wright, H.: J. M. Research **13**:349, 1904.

16. Lord, F. T.: J. A. M. A. **55**:1261, 1910.

17. Naeslund, C.: Acta path. et microbiol. Scandinav. **2**:110, 1925.

18. Lichtenstein, B. W., and Zeitlin, H.: J. A. M. A. **106**:1057, 1936.

Various causative organisms have been described under different names in the literature: Streptothrix, Cladothrix, Actinomyces, Nocardia, Actinocladothrix, Micromyces, etc. These differences in the nomenclature are probably due to the difficulty in culturing the organisms and to their tendency to vary morphologically. The term Nocardia has been dropped, and all the forms, including the genus, are classified under the genus Actinomyces. The genus has been placed in the family Actinomycetaceae.

In our case the typical ray colonies with their cortical and medullary zones were not demonstrable.

## SUMMARY AND CONCLUSION

A case of actinomycotic abscesses of the brain secondary to a small focus in the lung is described.

Actinomycotic involvement of the central nervous system is secondary to a primary focus elsewhere in the body. Actinomycotic lesions described as primary in the central nervous system are probably metastatic.

In the absence of an obvious gross primary actinomycotic lesion it is advisable to study the lungs and other likely organs after previous fixation.

Histologically, the changes in the brain produced by actinomycotic infection are not specific, in no way differing from those produced by an ordinary abscess.

# Laboratory Methods and Technical Notes

## INFRA-RED PHOTOGRAPHY OF GROSS ANATOMIC SPECIMENS

Leo C. Massopust, Milwaukee

Owing to the lack of color contrast in some tissues, the results obtained with ordinary photographic materials and methods have been most discouraging. For example, in some types of pathologic lung tissue it is almost impossible to demonstrate photographically any of the color contrasts between the normal tissue and the tissue showing pathologic lesions.

The purpose in this paper is to present a simple photographic technic which will excellently reveal details of structure in some tissues in which the ordinary photographic methods fail to do so.

### MATERIALS AND METHODS

The Eastman infra-red plate type 1R is used in conjunction with any ordinary camera and lens. The only additional equipment necessary is the Wratten no. 25 filter. It is advisable to focus the image on the ground glass of the camera with this filter in place over the lens. The specimen is immersed in water and illuminated with two 500 watt tungsten bulbs placed at a distance of about 36 inches (91 centimeters). The angle of the illumination will be determined by the type of specimen and by the photographic effect desired. The infra-red plate is handled and developed in total darkness. I have discussed the materials and methods used in infra-red photography in four previous publications.[1]

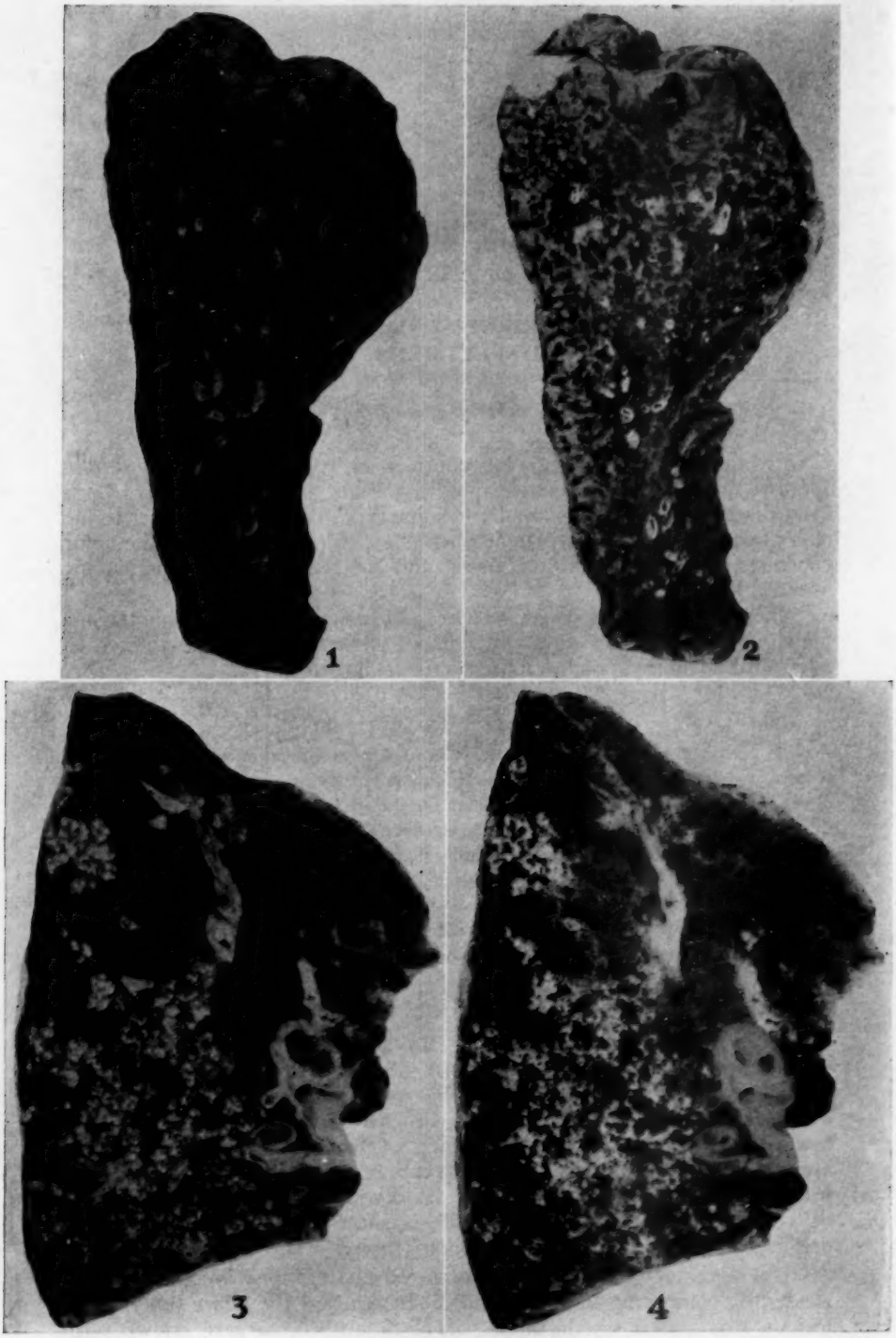
### ADVANTAGES OF METHOD

In the ordinary photograph (fig. 1) it is difficult to distinguish the normal lung tissue from the areas of silicotic change. On close visual inspection of the specimen it can be seen that there is present some anthracosis in the silicotic places, with an increase of these deposits toward the distal portion of the lung. Obviously these darker areas are recorded in the infra-red photograph as a deep black (fig. 2). This infra-red photograph demonstrates vividly the increase in the amount of contrast obtainable in tissue which shows little difference in the details of structure by ordinary photography.

The advantage of the use of infra-red photography is again demonstrated by comparing figures 4 and 3. In figure 4 the white tuberculous lesions superposed on the areas of black anthracosis are shown with greater clarity than they are in figure 3. The use of the infra-red

From the Department of Anatomy, Marquette University School of Medicine.

1. Massopust, L. C.: Radiog. & Clin. Photog. **10**:2-6, 1934; Anat. Rec. **61**: 71-79, 1934; Surg., Gynec. & Obst. **63**:86-80, 1936; J. Biol. Photographic A. **5**:20-24, 1936.



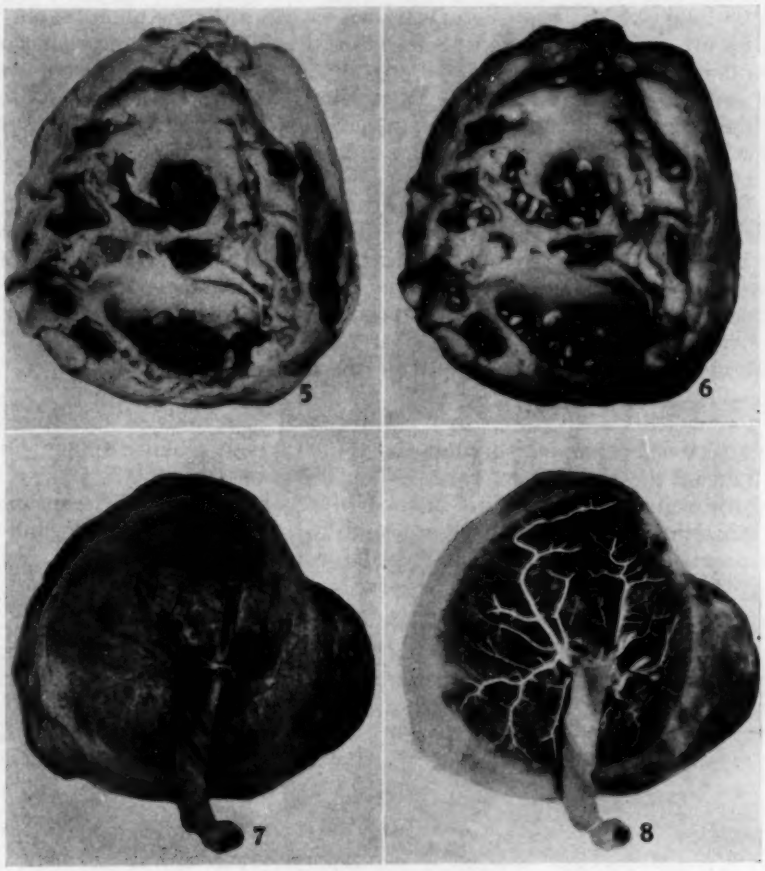

EXPLANATION OF FIGURES 1 TO 4

Fig. 1.—Silicotic lung. The specimen was immersed in water. Illumination was obtained from two 500 watt tungsten bulbs. The photograph was made on superspeed portrait film, with an exposure of one second.

Fig. 2.—Same specimen as shown in figure 1 photographed on Eastman infrared plate type 1R, with Wratten no. 25 filter and an exposure of ten seconds.

Fig. 3.—Tuberculous lung. The specimen was immersed in water. Illumination was obtained from two 500 watt tungsten bulbs. The photograph was made on superspeed portrait film, with an exposure of one second.

Fig. 4.—Same specimen as shown in figure 3 photographed on Eastman infrared plate type 1R, with Wratten no. 25 filter and an exposure of ten seconds.




EXPLANATION OF FIGURES 5 TO 8

Fig. 5.—Nephrolithiasis. The specimen was immersed in water. Illumination was obtained from two 500 watt tungsten bulbs. The photograph was made on superspeed portrait film, with an exposure of one second.

Fig. 6.—Same specimen as shown in figure 5 photographed on Eastman infra-red plate type 1R, with Wratten no. 25 filter and an exposure of ten seconds.

Fig. 7.—Human placenta. The arteries have received an injection of red cinnabar (mercuric sulfide) and the veins an injection of a mixture of red cinnabar and black india ink. The specimen was immersed in water. Illumination was obtained from two 500 watt tungsten bulbs. The photograph was made on superspeed portrait film, with an exposure of one second.

Fig. 8.—Same specimen as shown in figure 7 photographed on Eastman infra-red plate type 1R, with Wratten no. 25 filter and an exposure of ten seconds.

plate in this case produces somewhat of a plastic effect and again demonstrates an increase of the particles of coal toward the distal portion of the lung, which is not clearly shown in the ordinary photograph.

Figure 6 is the infra-red photograph of a kidney showing numerous calculi in the pelvis. In this photograph a decided improvement over the ordinary photograph (fig. 5) is shown in the color and outlines of the discrete calculi. This infra-red photograph also has a plastic effect. It shows definitely the shape and the surface markings of the calculi.

With infra-red photography unusually good definition of anatomic structure may also be obtained by injecting various color mediums into the blood vessels of a fresh specimen. Figure 7 is an ordinary photograph of a fresh human placenta into the arteries of which red cinnabar (mercuric sulfide) has been injected, while the veins have received an injection of red cinnabar mixed with black india ink. The method of making injections with mercuric sulfide is described by Swindle.[2]

On viewing a specimen that has received injections in this manner the arteries appear pinkish while the veins take on a bluish tinge. Thus in figure 8 the arteries are recorded on the photographic print as white and the veins as black. This method of recording color differentiation is valuable both in the immediate study of the fresh specimen and in the acquisition of a permanent record for future reference.

## CONCLUSION

With infra-red photography very slight differences in the color and morphologic detail of gross anatomic specimens may be recorded with excellent contrast.

2. Swindle, P. F.: Ann. Otol., Rhin. & Laryng. **44**:913-932, 1935.

# General Review

## THE EXPERIMENTAL NEPHROPATHIES

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NEW YORK

CONTENTS



### INTRODUCTION

The relationship of experimentally produced renal lesions to Bright's disease is still a major concern of present day pathology, even though the problem has for years held the attention and interest of numerous investigators. Attempts to reproduce the human disease in order to ascertain its etiology have been numerous, and many methods of attack and varieties of agents have been enlisted. Within the last decade the study has gained even greater impetus because of the immunopathologic implications, and a number of enthusiastic reports have been made in this connection.

It is the purpose in this paper to review briefly the various important attempts to produce renal disease. Comprehensive reviews were made by Leiter and by MacNider in 1924. MacNider also included a discussion of the functional effects observed in such studies.

The earlier investigations are presented in tabular form, the table being compiled mainly from the papers of MacNider, Leiter, Lyons, and Roth and Bloss. Since 1924, surveys of the literature on experimentally induced lesions of the kidney have been made by various authors. These, however, have not been inclusive since they were

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usually presented in relation to special results in particular fields of the problem. The following survey will concern itself for the most part with the experimental studies since that year of the type outlined in the table of contents for the purpose of clarifying and condensing this subject on which a voluminous literature has been built. A discussion of the changes effected by transplantation of the kidney, removal of renal substance, glomerular infarction, ligation of blood vessels and renal trauma was not considered germane to this review.

## SPONTANEOUS RENAL LESIONS OF COMMON LABORATORY ANIMALS

A proper evaluation of the morphologic results of any experimental procedure can be made only after a consideration of the spontaneous lesions. Again and again, changes attributed to a particular agent employed in an attempt to reproduce the human disease have been nothing more than the results of a spontaneous disturbance.

Spontaneous renal disease of animals has been familiar to pathologists for many years. The most commonly observed is the interstitial variety. In the review of experimental kidney disease by Roth and Bloss in 1922 a thorough survey of spontaneous lesions was undertaken. Their study disclosed an extremely high incidence of so-called interstitial nephritis, particularly in dogs and rabbits; it varied from 10 to 90 per cent, with an average of 40 per cent. In the earliest stage this lesion consisted grossly in radial yellow streaking of the cortex and later pitted depressions. Microscopically there were round cell infiltration (plasma cells, lymphocytes), later interstitial fibrosis with secondary atrophy of tubules and glomeruli, and finally replacement fibrosis. True glomerulonephritis, on the other hand, was observed but rarely.

The interstitial nephritis described by Roth and Bloss has been noted with great frequency since that time, perhaps more often in older dogs and rabbits. Leiter, who also referred to this phase of the problem, found spontaneous interstitial nephritis in 72 of his 133 rabbits, while MacNider found this lesion in 14 of 86 dogs. Henschen mentioned, in addition to interstitial lesions, degenerative nephrosis in dogs and cats.

Joest discussed other varieties of spontaneous interstitial lesions, namely, serous, hemorrhagic and purulent. Interstitial serous nephritis is characterized by kidney enlargement, edema of the interstitium and occasional infiltration by leukocytes and red blood cells. Hemorrhagic interstitial nephritis, on the other hand, shows frequent collections of red blood cells and polymorphonuclear leukocytes in the interstitium, while the purulent type consists of focal or diffuse interstitial infiltration by polymorphonuclear leukocytes. The last-named condition is either hematogenous or ascending in origin, very common and often associated with parenchymal necrosis and abscess formation.

Spontaneous true glomerulonephritis and glomerulitis are exceedingly rare (Roth and Bloss; Jaffé; Joest). Sporadic instances of glomerulonephritis in animals, however, have been reported in the literature. Mallory and Parker noted diffuse proliferation of glomerular endothelium, frequent mitotic figures and tuft enlargement in rabbits. Formerly these changes had been attributed to the action of zinc (Mallory and Parker, 1925), but subsequently they were considered to be spontaneous. Jaffé found spontaneous chronic diffuse glomerulonephritis in a rat and described a morphologic picture quite similar to that found in man. There were enlargement of the glomerular tufts, endothelial hyperplasia, capsular proliferation, hyalinization of glomerular tufts, atrophy of tubules, interstitial fibrosis and arteriolar thickening. Wells, in his discussion of Jaffé's presentation, remarked that he had observed in Maud Slye's collection a number of mice with glomerulonephritis, enlargement of the heart and hydrothorax.

Helmholz reported focal glomerulitis with polymorphonuclear exudation and fibroblastic proliferation in 2 rabbits.

Sheehan observed two types of spontaneous renal lesions in rabbits. He encountered the changes mentioned in 5 per cent of his animals. A different type of spontaneous lesion, usually diffuse, was found, however, in 8 per cent of his rabbits. In this group the epithelium of the cortical distal convoluted tubules was flattened, and the tubules were dilated. This is of considerable importance in the interpretation of experiments reported in this paper in the section dealing with lesions produced by excessive ingestion of protein or irradiated food products. Occasional dilatation of the proximal convoluted tubules and fibrosis of the interstitium were seen, and rarerly, calcified tubular casts.

Degeneration of the tubules has been known to occur rather frequently in rats, rabbits, mice and guinea-pigs (Jaffé; Joest) and most often is the accompaniment of infections and nutritional deficiencies. Calcareous tubular casts have been commonly observed to occur spontaneously, while hyaline droplet degeneration has been claimed to be a frequent consequence of circulatory disturbances and interstitial nephritis. Amyloid degeneration of the structural units of the kidney, on the other hand, is an unusual finding.

## LESIONS PRODUCED BY INORGANIC AND ORGANIC CHEMICAL COMPOUNDS

During the last decade the study of the effect of chemical agents on the kidney has been pursued with especial reference to renal immunity and the response of the glomerular tufts to such injury. Although regeneration of renal epithelium and resistance of epithelium to poisons had been observed in man and animals (Suzuki; Oliver; Aschoff), the

*Lesions Produced by Chemical Compounds*

| Author | Animal | Substance | Changes in Glomeruli | Changes in Tubules | Changes in Interstitium |
|---|---|---|---|---|---|
| Pavy, 1860 | Dog, rabbit | Mercury bichloride | None | Necrosis of epithelium | |
| Leyden and Munk, 1862 | Rabbit | Sulfuric acid | | Marked degeneration | Fibrosis; cell infiltration |
| Kabierski, 1880 | Rabbit | Chromates | Insignificant | Necrosis of epithelium | |
| Litten, 1881 | Rabbit | Sulfuric acid | | Marked degeneration | |
| Eliascoff, 1883 | Rabbit | Cantharidin | | Necrosis of epithelium | |
| Burmeister, 1883 | Dog | Sulfuric acid | | Marked degeneration and necrosis | |
| Cornil and Brault, 1884 | Rabbit | Cantharidin | Capsular space filled with cellular and albuminous débris and leukocytes, with compression of tufts; capsular epithelium swollen | Degeneration; desquamation; occasional necrosis | Perivascular round cell infiltration |
| Mürset, 1885 | Rabbit | Aloin | Epithelial degeneration | Degeneration of epithelium of convoluted tubules | |
| Welch, 1886 | Rabbit, white rat | Cantharidin | Accumulation of cells derived from tubular epithelium within subcapsular spaces | Degeneration | |
| Hellen and Spiro, 1897 | Rabbit | Tartrates | Paralysis of capillaries; obliteration of subcapsular spaces | Degeneration of convoluted tubular epithelium | |
| Flexner, 1897 | Guinea-pig, rabbit, mice | Ricin and abrin | Increase in polymorphonuclears; epithelium degenerated | Severe degeneration and necrosis; hyaline droplets | |
| Harnack and Kustermann, 1898 | Cat | Mercury bichloride | | Fatty changes of epithelium | Round cell infiltration |
| Karvonen, 1898 | Rabbit, dog | Mercury bichloride | Glomerular congestion; desquamation of endothelium and capsular epithelium | Foci of necrosis | Perivascular cellular infiltration |
| Richter and Roth, 1899 | | Cantharides | Dilatation of capillaries; infiltration of capsule by polymorphonuclears | Degeneration (late) | |
| Lyon, 1904 | Cat | Mercury bichloride | Congestion; swelling of capsular epithelium; cellular masses within subcapsular space | Swelling; granular degeneration; necrosis; calcification | Congestion of intertubular capillaries; perivascular round cells |
| | Rabbit | Cantharides | Endothelium intact; swelling of capsular epithelium | Necrosis | Congestion of intertubular capillaries; foci of round cells and necrosis |

| | | | | | |
|---|---|---|---|---|---|
| Harrington, 1904 | Cat | Sodium borate | | Marked epithelial degeneration; hyaline casts | Foci of round cells and necrosis |
| Petroff, 1905 | Rabbit, guinea-pig | Salts of mercury, copper, zinc, iron, argentum, phosphorus, arsenic | | Necrosis | Proliferation |
| Schlayer and others, 1907, 1909, 1913.. | Rabbit | Potassium dichromate | Exudate in capsular spaces | | |
| | | Mercury bichloride | | Degenerative lesions (severe) | |
| | | Cantharides | | | |
| | | Arsenic | Dilatation of blood vessels | | |
| Ophüls, 1907 | Dog | Potassium dichromate | | Necrosis and desquamation of tubular epithelium | |
| Christian et al., 1908, 1911, 1913..... | Rabbit | Uranium nitrate | Hyaline droplets in capillary endothelium | Epithelial degeneration | |
| | Guinea-pig | Uranium nitrate, potassium dichromate | Fibrinous thrombi in capillaries; hemorrhages in tufts; endothelial and occasional epithelial proliferation | | After repeated doses, focal scars with round cell infiltration |
| Dickson, 1909, 1912 | Guinea-pig | Uranium nitrate (repeatedly) | Dilated capillaries; thickening of capsule; hyaline degeneration of basement membrane | | |
| Pearce, 1910 | Dog | Uranium nitrate | | Epithelial degeneration | |
| Pearce et al, 1910..... | Dog | Potassium dichromate, uranium nitrate, mercury bichloride | | Epithelial injury | |
| Folin, Karsner and Dennis, 1912..... | Cat | Uranium, potassium dichromate, cantharidin | Slight | Severe tubular injury | |
| Aschoff, 1912 | | Mercury bichloride, cantharidin, uranium nitrate | None | Swelling; hyaline vacuolation; necrosis | |
| MacNider, 1912, 1913, 1914..... | Dog | Uranium, anesthetics, diuretics | Slight injury | Severe injury | |
| MacNider, 1912 | Dog | Arsenic | Paralysis of capillaries (dilatation) | Convoluted tubular epithelium injury (late) | |
| MacNider, 1912 | Dog | Potassium dichromate | Slight glomerular engorgement | Degeneration primarily | |
| | | Uranium nitrate | Primarily capsular engorgement—questionable of tufts | Epithelial degeneration; swelling; desquamation; many casts | |
| | | Sodium arsenate | No changes described | | |
| Boycott and Ryffel, 1912..... | | Potassium dichromate, mercury bichloride, uranium | | Degeneration of epithelium of convoluted and Henle portions | |

*Summary of Observations Recorded to the End of 1924—Continued*

| Author | Animal | Substance | Changes in | | |
|---|---|---|---|---|---|
| | | | Glomeruli | Tubules | Interstitium |
| O'Hare, 1913 | Rabbit | Bacillus coli, uranium | Occasional proliferation of endothelium; thickening of capsule | | Scarring |
| Chisholm, 1913, 1914, 1915 | Rat | Uranium Potassium dichromate | | Extensive tubular necrosis | |
| Baehr, 1913 | Rabbit | Uranium nitrate | Coagulation necrosis of capillaries; formation of syncytium from capsular epithelium; secondary canalization of glomerular mass by new capillaries; hyaline changes in tuft with capsular adhesions | | |
| Underhill, Wells and Goldschmidt, 1913 | | Tartrates | None | Necrosis of epithelium of convoluted tubules | None |
| Wiesel and Hess, 1914 | Rabbit | Uranium nitrate and epinephrine | Swelling, hemorrhage and exudation into glomeruli; later proliferation, organization and contraction | | |
| MacNider, 1914 | Dog | Uranium nitrate | | Epithelial degeneration | |
| Oliver, 1915 | Rats, guinea-pigs, rabbits | Uranium nitrate Chromate, sublimate | Pyknosis of endothelial cells | Epithelial degeneration mainly of proximal tubule | Proliferation |
| Bell et al., 1915 | | Tartrates | | Severe necrosis of epithelium of convoluted tubules | |
| Major, 1917 | Rabbit | Uranium, Staph. aureus | Varying destruction and fibrosis of glomeruli; round cell infiltration | | |
| MacNider, 1920 | Dog | Uranium nitrate, mercury bichloride | Fibrosis | Acute degeneration of epithelium of convoluted tubules; replacement by flat type of cell | |
| Roth and Bloss, 1922 | Rabbit | Uranium nitrate and ephedrine | Occasional hyaline droplet of endothelium | Marked degenerative lesions | |
| Frandsen, 1924 | Rabbit | Uranium | Acute—hyperemia; capsular epithelium desquamated | Degeneration of epithelium, especially convoluted | Hemorrhage |
| | | | Chronic—atrophy; periglomerular tissue proliferated | Degeneration and necrosis | Proliferation |
| | | Chromates | Atrophy (secondary to other changes) | Degeneration; necrosis of epithelium | Diffuse proliferation; cellular infiltration; recent hemorrhage |

*Lesions Produced by Bacteria and Bacterial Toxins*

| | | | | | |
|---|---|---|---|---|---|
| Babes, 1890 | Rabbit | Diphtheria bacilli | Leukocytes with fragmented nuclei in capillaries; karyokinetic figures in endothelium of glomerular capillaries and in capsular epithelium; "hyaline" swelling of vessel wall | Degeneration | |
| | | Diphtheria toxin | | Parenchymatous degeneration with disappearance of nuclei | |
| Welch and Flexner, 1891 | Cat | Diphtheria bacilli or toxin | Hyaline swelling of glomerular capillaries and small arteries | Fatty changes | |
| Pernice and Scagliosi, 1894 | Rabbit, dog, guinea-pig | Anthrax, B. pyocyaneous, B. prodigiosus, Staph. aureus | Hyperemia and hemorrhage<br>Cellular degeneration<br>Atrophy | Parenchymatous degeneration<br>Casts | Proliferation |
| Morse, 1896 | Rabbit | Staphylococcus (dead) and toxin | | Injury of epithelium | Hyperplasia (marked) |
| Lubarsch, 1897 | Dog, rabbit | Staph. aureus (living) | Amyloid changes in vessels | | |
| Flexner, 1897 | Rabbit, guinea-pig, kitten | Diphtheria toxin | Necrosis of endothelial cells of capillaries with leukocytic infiltration | Degeneration<br>Occasional calcium deposition | |
| | | Diphtheria and streptococcus toxin | Degeneration of epithelial elements | Necrosis; degeneration | |
| Lyon, 1904 | Rabbit | Diphtheria toxin | Congestion of blood vessels with occasional hemorrhage; early dilatation of loops with thrombus formation; endothelial swelling; leukocytes in capsular space | Degenerative changes; occasional necrosis | |
| LeCount and Jackson, 1914 | Rabbit | Streptococcus | Fibrinous thrombi; hemorrhage in glomerular space | | Perivascular lymphocytic and plasma cell exudates; focal scars |
| Frothingham, 1914 | Rabbit | Diphtheria toxin | None | None | |
| Klotz, 1914 | Rabbit | Str. viridans | Acute and chronic interstitial nephritis—spontaneous? (H. H.) | | |
| Pappenheimer, Hyman and Zeman, 1916 | Rabbit | Str. haemolyttieus | Increase in polymorphonuclears; engulfed organisms; hyaline thrombi in capillaries; periglomerulitis; later lesions more focal with swelling and hyalinization of capillary wall | Slight degeneration | |
| Stoddard and Woods, 1916 | Rabbit | Streptococcus and staphylococcus toxins | | Marked degeneration | |
| Major, 1917 | Rabbit | B. mucosus-capsulatus | Hyaline and fibrinous thrombi in capillaries; erythrocytes in spaces | Marked degenerative changes | |
| Ophüls and Smith, 1917 | Rabbit | Streptococci | Thrombi; necrosis; adhesions | Degeneration; red cells | Focal round cells |

*Summary of Observations Recorded to the End of 1924—Continued*

| Author | Animal | Substance | Changes in | | |
|---|---|---|---|---|---|
| | | | Glomeruli | Tubules | Interstitium |
| Winternitz and Quimby, 1917..... | Dog | B. bronchisepticus | Cellular increase; adhesion to capsule | Necrosis; casts | Chiefly round cell infiltration; scars |
| Bailey, 1917 ..... | Rabbit | Diphtheria toxin alone or with pituitary extract | Swelling and desquamation of endothelial cells; fibrinous thrombi; hyaline masses in necrotic capillaries of tufts, with hemorrhage | | |
| Faber, 1917 ..... | Rabbit | B. coli, diphtheria toxin | Capsular space—fibrin, red blood cells and desquamated epithelium; also fibrin within glomeruli; leukocytes | | |
| Faber and Murray, 1917..... | Rabbit | Str. haemolyticus<br>Str. viridans, B. coli<br>Staphylococcus | Endothelial swelling<br>Congestion<br>Ischemia—sporadic and focal | | |
| Bloomfield, 1919 ..... .... | Rabbit<br>Left renal vein | Str. haemolyticus and Str. viridans (dead); 1 week later repeated intravenous injection | None | None | None |
| Kuczynski, 1920 ..... | Mice | Streptococci | Degeneration followed by proliferation and hyalinization (latter often seen normally in mice) | | |
| Dibbelt, 1922 ..... | Mouse, guinea-pig | Pasteurella avisepticus, anthrax bacillus | Endothelial proliferation; increase of polymorphonuclear cells; swelling of capillary wall (focal) | Degenerative changes (proximal convoluted portions) | |
| Wolff, 1922 ..... | Mouse | Diphtheria bacilli | | Degenerative changes | |
| Kinsella and Sherburne, 1923..... | Dog | Str. viridans | Partial thrombosis of tuft; hyaline degeneration; hemorrhage; polymorphonuclear infiltration | (Also endocarditis) | |
| Takenomata, 1923 ..... | Rabbit | Streptococcus (scariatina) | Thickening of capillary loops; cellular proliferation; partial or complete necrosis; increase in polymorphonuclear cells | Degenerative changes | |
| Leiter, 1924 ..... | Rabbit | Diphtheria toxin, Str. viridans | Hyperemia and dilatation of capillary; endothelial degeneration; occasional thrombi in loops; blood cysts | Severe degeneration | |
| | | Str. viridans (alone) | Occasional infarcts in kidneys associated with endocarditis; no other renal lesions of note | | |
| | | Str. viridans (intracardiac) | None | None | |
| | | Str. viridans and spores of Lycopodium into renal artery | Infarcts, thrombi in vessels; pericapsular fibrosis | ..... | Interstitial fibrosis; perivascular lymphocytic proliferation |

*Lesions Produced by Parenteral Administration of Proteins*

| | | | | | |
|---|---|---|---|---|---|
| Sollman and McComb, 1898..... | Rabbit | Extract of rabbit muscle | ..... | Epithelial degeneration | |
| Sollman and Brown, 1901-1905..... | Rabbit | Proteins | ..... | Cloudy swelling and vacuolation of cells of convoluted tubules | |
| | Dog | Proteins | None | None | |
| Longcope, 1913 ..... | Cat, dog, rabbit, guinea-pig | Protein | Hyaline degeneration in scattered tufts | Cloudy swelling | Round cells; increase of connective tissue |
| Woolley et al., 1914..... | Guinea-pig | Protein | Albuminous exudate in spaces | Cloudy swelling | Fibrosis; lymphocytes |
| | | | (Changes considered insignificant) | | |
| Boughton, 1916 ..... | Guinea-pig | Protein | Hyperemia; occasional hemorrhage (focal) | Necrosis; cloudy swelling; desquamation (focal) | Round cells (focal) |
| Stoddard and Woods, 1916..... | Rabbit | Vaughan's split protein | ..... | Necrosis of convoluted tubules | |
| Coulter and Pappenheimer, 1916..... | Rabbit | Egg white sensitization followed by injection of egg white into renal artery | Endothelial swelling and proliferation (focal) | | |
| | | Sensitization to bacterial proteins followed by injection of these bacteria into renal artery | Löhlein-Baehr lesions (thought due to bacterial bodies) | | |
| Faber, 1917 ..... | Rabbit | Vaughan's split protein | Fibrin, erythrocytes and desquamated epithelium in capsular space; fibrin in glomerular tufts | | |

*Lesions Produced by Snake Venom*

| | | | | | |
|---|---|---|---|---|---|
| Pearce, 1909 ..... | Rabbit | Snake venom | Hemorrhages into tufts; exudation of serum and fibrin; capsular epithelium not damaged | | |
| Pearce, 1913 ..... | Rabbit | Snake venom | Proliferation of endothelium plus foregoing changes | Degeneration | |
| | Dog | | Hyaline changes in capillaries | | |
| Suzuki, 1921 ..... | Rabbit | Snake venom | Capillary "cysts" containing thrombi; endothelial proliferation; degenerative arteriolar changes | Atrophy | Fibrosis (late) |
| Acki, 1924 ..... | | Snake venom | Epithelial cell proliferation; proliferation of fibroblasts | | |
| Leiter, 1924 ..... | Rabbit | Snake venom | No significant changes except endothelial degeneration | | |

nature and the development of the immunity was first systematically investigated by Gil y Gil. This worker found that repeated small doses of uranium and mercury bichloride could induce tolerance of the epithelium for the poisons. However, such immunity was found to be distributed unequally, for while one portion of the tubular tree appeared resistant, another exhibited intense degenerative changes. The distal segments of the convoluted renal tubules were found more sensitive and immunity to the poisons in these segments usually developed more rapidly. Two animals disclosed no recent tubular changes, although amounts of uranium had been administered which ordinarily elicited a pronounced reaction in normal animals. The glomerular lesions of normal animals described previously were observed and consisted of epithelial degeneration and occasional loop necrosis. In the immune animals, on the other hand, there were no notable glomerular changes. In a similar but less extensive study Jessen found regeneration of tubular epithelium in the third and fourth segments of the proximal convoluted tubules of rabbits which had been given uranyl (uranium dioxide) acetate by hypodermoclysis. There were, in addition, interstitial fibrosis and lymphocytic infiltration.

In 1928 W. C. Hunter, stimulated by the work of Gil y Gil, also undertook the study of the mechanism of the acquired resistance of tubular epithelium to uranium nitrate. In rabbits acutely poisoned with small doses, he found epithelial necrosis in the distal and transitional segments of the proximal convoluted tubules. With larger doses, the tubular injury extended into the medial segment and was associated with fatty degeneration. The glomerular capillaries were frequently congested, with concomitant swelling of the glomerular epithelium. With still larger doses, the tuft changes were more pronounced and consisted of capsular adhesions, filling of the capillary lumen with fibrin, cystlike hemorrhages in the glomeruli and interstitial edema. Several days after administration of the drug, evidence of regeneration and occasionally crescents appeared. The latter were believed to be due to repair. It is of extreme interest that in the experiments on immunity from 54 to 96 times the original dose was given without damage to the regenerated cells or glomeruli.

In 1929 Hunter demonstrated that renal tissue of rabbits may also acquire resistance to mercury bichloride. The lethal dose was found to be 0.015 Gm. subcutaneously and 0.003 Gm. intravenously. Rabbits that died after receiving subcutaneous injections showed parenchymatous degeneration of the tubular epithelium but little actual necrosis; the glomeruli showed slight swelling and epithelial desquamation. With higher doses, 0.015 to 0.02 Gm., necrosis of the convoluted epithelium was noted. The cystlike intraglomerular hemorrhages seen commonly

in uranium poisoning were rare. In general, the glomerular injury was less intense than that usually found in the uranium-poisoned kidney. The regenerated tubular epithelium consisted of flattened, elongated cells with hyperchromatic nuclei and bluish pink cytoplasm. Between injections time for recovery was allowed in order that the variety of changes due to subsequent treatment might be ascertained. One administration of the drug was made by either the subcutaneous or the intravenous route. In spite of the inconstancy of the results, the study seemed to indicate that the regenerated tubular cells were somewhat resistant and did not show the severe degenerative lesions which the original cells did. Such a study was hampered, the author pointed out, by the inconstancy of the quantity of mercury absorbed (due to local corrosive action and to irregularity of absorption and excretion by the intestines, with resultant enterocolitis).

In 1926 Suzuki studied the effect of subcutaneous injections of uranium nitrate on the kidneys of rabbits especially in order to ascertain the nature of the glomerular injury. He reported epithelial swelling in the tuft and capsule and thickening of the capillary wall, and he considered that the thickening of the loops was due to proliferation of the tissue between the endothelium and the basement membrane. An important rôle in the loop widening was also attributed to the epithelial cell hyperplasia. Hyaline droplets were occasionally seen within the epithelial cells. Subsequent glomerular collapse and secondary atrophy of the tubules occurred. Similar glomerular abnormalities were found in guinea-pigs, but in these animals the tuft changes were thought to be secondary to the tubular lesions. The explanation of this discrepancy was not made clear.

Dake injected uranium nitrate subcutaneously into rabbits and found pyknosis of nuclei or cellular enlargement of glomerular tufts and very occasional rupture of capillary walls. The tubules showed cloudy swelling and occasional necrosis of convoluted portions and of Henle's loops. The interstitium contained round cell infiltration.

MacNider in 1917 had shown that the nephrotoxic and general toxic effects of uranium were more pronounced in older animals. That gestating animals were highly susceptible to uranium nitrate was demonstrated by MacNider, Helms and Helms. The animals received one subcutaneous injection of uranium nitrate. Despite the increased sensitivity of pregnant dogs to uranium, recovery was found to occur. Two dogs of a group of animals that recovered were killed for the purpose of histologic study. These dogs revealed reparative processes, as evidenced in the glomerular tufts by nuclear hypertrophy and areas of regenerating tubular epithelium and mitoses. Coalescence of loops with occasional obliteration and capsular thickening were also found. The

tubular epithelium, particularly that of the convoluted portions, was swollen and vacuolated, and the nuclei were poorly stained, whereas others showed regeneration. The cells contained mitotic figures, or the epithelium had been replaced by cells of a low, flattened type. Liver changes were observed which were occasionally much more severe than the changes found in the kidney.

A second group of animals clinically manifested signs of lesions in both the liver and the kidney. At autopsy they showed lesions in the liver which were more severe than those in the kidney. Even here, however, there were vacuolation, necrosis and swelling of the tubular epithelium, largely confined to the convoluted tubules and in only 1 of the 5 animals in this group was there any evidence of repair.

In 1929 MacNider, in a study undertaken to ascertain the nature of the atypical syncytial regenerated tubular epithelium mentioned, attempted to determine by subsequent injections if there was a difference in reactivity of the various types of epithelium to uranium nitrate. A second dose of the poison was given to dogs at three different stages of their reactions to the primary injection: (1) during the course of acute "nephritis"; (2) after the animals had returned to a normal functional state; (3) after the picture of chronic nephritis had developed. In the first group the animals quickly succumbed and showed an intensification of the degenerative process. In the second group, also, there was an increased susceptibility to the drug, with no evidence of atypical tubular cells. There were glomerular endothelial hypertrophy, occasional hyperplasia, thickening of the capsule and early formation of connective tissue. The group with the chronic condition, however, was found to be resistant. Histologic studies indicated that repair of degenerated convoluted tubular epithelium occurred either from cells which were not entirely destroyed or from the aforementioned atypical syncytial cells. MacNider felt that resistance resided mainly in the atypical epithelial cells and that repair occurred by an ingrowth of these peculiar cells and from noninjured epithelial cells.

A second study of the clinicopathologic course of the "nephritis" induced in dogs by uranium nitrate was reported by MacNider in 1929. Animals were given a single subcutaneous injection of a dose of the salt equal to 4 mg. per kilogram. Depending on their reaction, the animals were divided into three groups. In the first group (dogs over 7 years of age which died or were put to death during the acute stages) there was primarily an extensive degeneration of the epithelium of the proximal convoluted tubules. The glomerular capillary endothelium was prominent, and the capillaries were engorged. In the second group (young animals that returned to a normal functional state after the development of "acute nephritis") biopsy showed that the renal lesion

early in the experiment was similar to but less severe than those just described. These animals when subsequently put to death showed repair of the tubular epithelium with frequent mitoses. Many of the glomeruli were increased in size as a result of thickening of the capillary walls and endothelial hyperplasia. There was fibrous replacement of a few tufts, while others were hyperemic. Occasional adhesions of the loops to the capsule, with thickening of the latter, were also seen. The third group consisted of animals which failed to return to a normal functional state after the development of "acute nephritis." The kidneys of this group were decreased in size. Microscopically there was glomerular and capsular fibrosis of various degrees. The smaller arteries were thickened, and the tubules were partially replaced by connective tissue. In regard to the question of tubular repair, it is especially noteworthy that histologic preparations of these kidneys revealed two different varieties of epithelial cells in the proximal convoluted segments: (1) granular, degenerating cells with occasional mitotic figures; (2) flat cells with prominent nuclei, which occasionally resembled a syncytium. A review of the detailed clinical study was also made, but it is obviously beyond the scope of this paper.

Hunter and Roberts similarly investigated the glomerular changes in the kidneys of rabbits and monkeys induced with uranium nitrate, mercury bichloride and potassium bichromate. In the acutely poisoned (uranium) rabbits (given one or at most two subcutaneous or intravenous injections of uranium) they described necrosis of the epithelium of the proximal convoluted tubules. The glomeruli revealed cellular necrosis, swelling and desquamation of the capsular epithelium, ischemia, intraglomerular hemorrhages and many a decrease in cellular content. There were also hyaline droplets in the capillary walls and in the epithelial cytoplasm. The basement membrane (azan-carmine stain) was often fragmented or beaded. This was also found associated with intraglomerular hemorrhage. In animals which had received increasingly larger doses over a period of several months there were atrophy and ischemia of the glomerular tufts, dilatation of the capsular space, hyperplasia of the capsular epithelium with occasional crescent formation, thickening of Bowman's membrane and hyaline droplet degeneration. The changes of the basement membrane were similar to but more marked than those in the acute stages.

Glomerular injury following intoxication with mercury bichloride was less frequent. In some acute lesions there were beading and fragmentation of the glomerular membrane and diminution of cells. In all but 1 of 10 rabbits which had received repeated doses of the drug there was beading of some degree, while thickening of the basement membrane

was less common. In chronic mercurial injury the glomerular epithelium occasionally showed evidence of regeneration and in several instances was proliferated.

Potassium bichromate produced necrosis of tubules and acute degeneration in the kidneys of rabbits. The glomerular changes consisted only of fragmentation of the basement membrane. In 6 monkeys there were similar effects but less pronounced changes of the basement membrane. The changes in the tubules were not described.

The authors concluded from these studies that the renal lesions induced by chemical poisons are primarily glomerular and that the alterations in the basement membrane are degenerative and permanent.

Ishiyama reported the results which he obtained in rabbits' kidneys by injections of uranium nitrate, mercury, cantharidin and Habu snake venom. His study is primarily of physiologic interest. The snake venom was injected intravenously, while the other poisons were administered subcutaneously. Uranium produced enlargement of the glomeruli and engorgement of the tuft capillaries. The capsular spaces, nevertheless, were often enlarged. The tubular epithelium, especially that of the intermediate segments, was swollen and showed fatty changes. Hyaline casts, hyperemia and occasionally an interstitial increase were also observed. With mercury and cantharidin similar findings were noted, except that there was also seen endothelial hyperplasia. In the kidneys injured by mercury, in addition, the tubular changes were more pronounced, with intense fatty change and occasional necrosis. Habu venom induced pronounced engorgement and slight fatty change of the tufts with interstitial hyperemia. The relationship of the duration of observation to the histologic changes was not made clear.

Gray in a general study of nephropathic agents described widespread tubular degenerative alterations following intoxication with cantharidin, lead nitrate, potassium bichromate and iron. Glomerular changes followed administration of cantharidin only and consisted of swelling of the parietal tuft epithelium; they were considered secondary to the tubular changes. Tubular degeneration alone occurred after intoxication with the other poisons, with no significant glomerular lesions.

The effect of mercury bichloride, potassium bichromate and uranium nitrate on the frog's kidney was studied by Oliver and Smith in 1930 in order to compare the results in this species with those found in mammals. Cloudy swelling of the tubular epithelium with occasional foci of necrosis and desquamation limited to the proximal convoluted tubules were produced by all poisons. The glomeruli showed depositions of granular material within the subcapsular space. Interstitial edema was also present. The more severe damage was evidenced by tubular necrosis, hyaline casts and cellular desquamation. The glomeruli

showed fibrinoid collections within Bowman's space and intense capillary engorgement with hyaline thrombi composed of agglutinated red cells. There were also scattered areas of edema and necrosis, also hemorrhage into the subcapsular space. Reparative processes with many mitotic figures were noted in 3 or 4 animals after injection. Regenerative evidences in the glomeruli appeared later. The authors were of the opinion that the lesion was primarily limited to the proximal convoluted tubules but that with increasing doses it involved the remainder of the nephron, and they concluded that lesions in the kidney of the frog differed only in degree from those found in the mammalian kidney.

In 1931 Oliver and Smith investigated the anatomic alterations induced in the isolated perfused (with oxygenated Locke's solution) frog's kidney by potassium bichromate, mercury bichloride, urethane and uranium nitrate. The epithelial lesions, as shown by mitochondrial preparations, revealed cloudy swelling of mitochondria, formation of irregularly clumped granules and lysis of granules (particularly after the use of mercury bichloride). There were also epithelial necrosis and desquamation. Based on the appearance of granular material within the capsular space and passage of dyes, increased permeability of capillary walls was believed to be the earliest glomerular lesion. Edema of the tuft followed, with pyknosis of nuclei, focal necrosis (especially after the injection of mercury bichromate) and appearance of fibrinoid material within the capsular spaces. Reactive phenomena were absent. The interstitial tissue was edematous. In summary, except for the absence of reactive changes the authors felt that the lesions resembled very closely those produced in the living animal.

In the following year Oliver reported further perfusion experiments on kidneys isolated from frogs, which were subjected to vascular and parenchymal disturbances in an effort to deduce the functional responses. He utilized the separate sources of the kidney's blood supply for this study (the glomeruli are mainly fed by the aortic branches, while vessels from the renal-portal system supply segment II of the tubules). Mercury bichloride was employed to produce parenchymal changes directly. In spite of almost identical functional responses, the pathologic pictures were vastly different. In the first group there were no remarkable histologic changes. In the second group, however, in which the poison was directed toward the glomeruli, he found areas of edema, necrosis and nuclear degeneration within the tufts. Bowman's space contained fibrinous deposits and desquamated epithelial cells. The tubular epithelium was not noteworthy after injection of the injurious substance into the aortic branches. Where this was directed toward the tubular epithelium there were cloudy swelling and agglutination of mitochondria and nuclear degeneration. There were no

functional differences between the two groups, although histologic preparations showed marked differences, as indicated, and led to the conclusion that "functional testing of the kidney cannot, therefore, suffice to determine the condition existing in the kidney."

The nature of the mitochondrial injury reported by Oliver is not quite settled. Moore, Goldstein and Canowitz observed the effect of mercury bichloride on the mitochondria in white rats. Their observations indicated that mitochondrial changes did not go hand in hand with cell injury. Parenchymatous degeneration of the convoluted tubules was observed to occur first, followed subsequently by agglutination and then fragmentation of mitochondria, with subsequent cell death. Moore and his co-workers believed that the poison was first absorbed by the mitochondria and injured the cells secondarily.

Interpretation of mitochondrial alterations is attended with great difficulty. Granularity of the mitochondria of the convoluted tubular epithelium was shown by Oliver (1915) to occur during diuresis alone. Smith and Rettie described granulation and clumping of mitochondria after ether and chloroform anesthesia, the injection of ammonium chloride, a ketogenic diet and the administration of sodium oxalate. The opinion was offered that these changes were the earliest indication of cell injury and concluded "that all degeneration (cloudy swelling and fatty degeneration) involved a destruction of mitochondria."

Cowdry in his review of the reactions of mitochondria to cellular injury made the significant point that granularity of mitochondria could not be regarded as a specific effect of any particular injury. "It is not even known whether these different modes of injury act directly on the mitochondria or whether the morphologic changes in them are merely the visible expression of a long line of interdependent chemical reactions in the cytoplasm: the latter interpretation has more to commend it."

A later study of the mitochondrial changes in nephritis caused by oxalate and uranium was reported by Gough. Rabbits given sodium oxalate or uranium acetate were put to death at intervals of from a few minutes to three hours after injection. Intense mitochondrial changes were noted, consisting of granulation and fusion. In the uranium-injured kidneys the mitochondria were replaced by spherical globules. Gough stressed the point that granularity and fusion of the mitochondria did not necessarily represent a permanent change, but he attached greater importance to the spherical globules observed in the uranium-poisoned kidneys.

Bodansky and his co-workers injected uranium acetate into pregnant rabbits and dogs in an effort to produce lesions in the fetus. Degenerative tubular changes in the young were described which cor-

responded somewhat to those found in the mother. Glomerular abnormalities, however, were less marked. Their report was of a preliminary nature and incomplete.

Vassiliadis reported experiments on rabbits in which he employed uranium nitrate, mercury bichloride, cantharides and bismuth. The lesions were corroborative of those previously reported and otherwise are of no especial interest.

Modell and Travell made the interesting observation that a redistribution of tubular fat occurred in an adult cat following administration of uranium. The normal large quantity of lipoid (Modell) in the convoluted renal tubule was also increased, with extension of the fat into Henle's loops. That the appearance of fat in Henle's loops was not a degenerative manifestation, the authors believed, was indicated by the absence of necrosis and of other degenerative changes in Henle's cells.

I. Sachs repeated and confirmed the work of Wiesel and Hess (table) in dogs, rabbits and guinea-pigs. Animals were given uranium nitrate either alone or associated with ephedrine. The histologic changes were generally more severe in the animals which received uranium in combination with ephedrine. In the animals given uranium nitrate alone there was slight to moderate tubular degeneration and infrequently cellular hyperplasia of the glomerular tufts. After both uranium and ephedrine, on the other hand, the tubular damage was more pronounced and the glomerular loops often fused. In addition there were capillary thrombi. The exaggeration of the uranium effect was considered the result of the vascular spasm superimposed on the toxic effect produced by uranium nitrate.

Oxalic acid and its derivatives have been used infrequently. Dunn, Haworth and Jones made the most recent attempt, in 1924, and reviewed the scant literature published prior to their study. For a more detailed review of the effect of the oxalates the reader is referred to their paper. Briefly, it might be mentioned that the significant findings reported previous to that publication were degenerative tubular changes associated with the frequent deposition of oxalate crystals and masses within the tubular lumen. Occasional swelling of the glomerular and capsular epithelium was also noted.

Dunn and his associates administered oxalates to rabbits intravenously. The animals which received either a single or a few doses presented epithelial necrosis mainly of the descending limbs of the convoluted tubules and less marked lesions of the more proximal portions. The authors felt that the deposition of calcium oxalate crystals was secondary to the necrotic changes. The glomeruli were frequently congested, and the subcapsular spaces contained granular material. Macroscopically the kidneys were generally enlarged and pallid, with

infrequent punctate hemorrhages. Repeated administration of moderate doses produced desquamation and replacement of tubular epithelium, which was followed by atrophy. The glomeruli after repeated injections showed no remarkable changes.

Necrosis of the distal tubular segments in rabbits' kidneys was induced by Dunn and Polson by the intravenous injection of uric acid (in the form of lithium mono-urate). The authors believed that the changes were due to a precipitation of uric acid in these segments.

Seegal produced acidosis in rabbits and dogs by administering varying quantities of tenth-normal hydrochloric acid, ammonium chloride and calcium chloride for periods ranging from eleven days to one year. Histologic preparations of the kidneys revealed swelling and vacuolation of the tubular epithelium, nuclear pyknosis and karyolysis, and tubular casts. In addition, the dogs showed spontaneous interstitial lesions. Seegal stressed the important association of acidosis with the production of experimental lesions and pointed out that with alleviation of the acidosis, regeneration of the injured epithelium and a return to normal could occur.

The effect and the mechanism of the action of lead carbonate on the kidney of the guinea-pig were described, and the literature on this subject was thoroughly reviewed, by Pejic. In view of the extreme variance of the results, the author classified the experimental reports prior to his presentation according to the primary nature of the injury recorded. Thus a perusal of the literature permitted the consideration of four concepts of the pathogenesis of such lesions:

1. Pathologic changes begin in the glomeruli and tubular epithelium, with secondary involvement of the interstitium and subsequent renal contraction.
2. Primary lesions occur in the blood vessels, with secondary changes in the remaining structural units.
3. The primary changes are parenchymatous, with secondary vascular abnormalities.
4. Only parenchymatous degeneration occurs consequent to the administration of lead.

Pejic's survey includes not only observations that are concerned with experimentally produced lesions but also those on lesions in human kidneys. The interpretation of the latter group is exceedingly difficult, and frequently, as Pejic pointed out, there were complicating arteriosclerotic changes. Pejic further commented on the possibility that the discrepancies were also due to the circumstance that different stages of the renal lesions may have been studied.

In Pejic's series, after the administration of lead carbonate the kidneys were usually found enlarged with smooth yellowish-white surfaces. One guinea-pig alone showed contracted kidneys. This animal lived longest, two hundred and two days, and received the greatest quantity of lead carbonate, a total of 7.28 Gm.

Microscopically, the earliest lesion described was fatty and parenchymatous degeneration of the tubular epithelium, particularly that of Henle's loops and the distal convoluted portions. The glomerular epithelium also showed degenerative changes. A few hyaline and granular casts were found occasionally, with calcium deposits within the casts, the tubular epithelium and the interstitial tissue. Vascular lesions were absent, while interstitial lesions were noted only in those animals which lived longest and which had received the greatest quantities of lead. During the entire length of the experiment—seven months—the outstanding changes were in the epithelial elements.

Benoit, following his observation of acute guaiacol poisoning with renal changes in a patient, investigated the effect of subcutaneous injections of this drug on the kidneys of rabbits. He reported only on acutely poisoned animals and showed ischemia of the glomerular loops and swelling of the capillary walls with associated diminution of the lumen. Peculiarly, the endothelial cells here were not noteworthy, whereas those in the loops otherwise unaffected were swollen. The capsular spaces contained some desquamated cells and an albuminous exudate. Severe degenerative changes of the tubular epithelium, especially of the terminal convoluted portions, and formation of hyaline and hemoglobin casts were found. He concluded that guaiacol, similar to uranium, is a glomerulotubular poison. Histologic examination of other viscera, when made, revealed no remarkable abnormalities.

Levrat and Badinand in their study of the toxicity of acriflavine in rabbits noted degenerative tubular lesions with desquamation and formation of casts but no glomerular changes.

Vallery-Radot and his associates in 1932 described severe degenerative tubular changes, especially of the convoluted segments, in rabbits following large intravenous doses of epinephrine. The authors believed the changes to be quite similar to those produced with mercury. The glomerular tufts were intact.

The dye, styrol quinoline compound no. 90, injected intraperitoneally or subcutaneously into rabbits by Sheehan, produced necrosis of the convoluted tubules and occasional thrombi in glomerular capillaries. Secondary interstitial fibrosis with tubular regeneration and atrophy of tubules and glomeruli were also observed in later stages. Sheehan attributed the alterations to the excretion and retention of the dye by the convoluted tubular epithelium.

Paunz, on the basis of the contention of Volhard and Becker that tyramine was causally related to hypertension, repeatedly administered a 1 per cent solution of the drug subcutaneously to rats and dogs. The animals were treated daily for periods varying from eight to fourteen months. The lesions which he described were undoubtedly interstitial, with scarring and secondary involvement of the glomeruli. The animals showed swelling and coalescence of the glomerular loops, some of which contained a hyalin-like material. In dogs there was also reduplication of the internal elastic lamella of the smaller vessels.

Vallery-Radot and his associates in 1933 gave rabbits intravenous injections of gold salts. They found that the site of localization was usually directly proportional to the dose administered and the duration of survival of the animal. In rabbits put to death less than twenty-four hours after a single injection, metallic granules were found in the basal portion of the tubular epithelium. After several injections the particles were larger, occasionally confluent and distributed throughout the cells of the convoluted portions. The lumen, too, often contained metallic particles. Later, regeneration of the tubular epithelium and fibrosis were described. The glomeruli, except for occasional congestion, were unaffected.

Lawson, Redfield and Boyce produced intense necrosis of tubular epithelium in guinea-pigs and rabbits by the administration of colloidal sulfur.

*Comment.*—In general, chemicals mainly affect the tubular system. The changes consist of widespread cloudy swelling, vacuolar and fatty degeneration, desquamation, necrosis and infrequently calcification of the tubular epithelium. With uranium, to a lesser degree and frequency with mercury bichloride, and least with potassium dichromate, glomerular lesions of a focal type may be produced. These consist of congestion, cellular degeneration,. fibrin thrombi of the glomerular capillaries, cystlike hemorrhages, loop necrosis, and thickening, fragmentation and occasional rupture of the capillary walls. Cellular proliferation, hyaline droplet degeneration, crescent formation, and ultimately atrophy and fibrosis of glomerular tufts have also been noted. The interstitial tissue frequently shows edema and proliferation. That epithelial immunity to uranium and mercury bichloride may be established has also been amply demonstrated. This has been shown to reside in an atypical syncytial epithelium.

That certain renal lesions occur following ingestion of the various poisons discussed in the foregoing section is too well known to merit comment here. In no way, however, do such lesions bear any resemblance to those observed in bilateral diffuse glomerulonephritis. Experiments of the nature reviewed are nevertheless of vital importance in the

determination of the toxic properties of chemical agents, the mode of excretion of such substances and the functional changes which they are able to produce. The etiologic significance of the various chemicals in relation to Bright's disease is, however, quite obviously remote.

### LESIONS PRODUCED BY IRRADIATION

Roentgen rays have been used to produce renal lesions with variable success. In common with chemical agents they produce changes which are unlike those seen in human glomerulonephritis. Irradiation is important, however, in the production of certain functional changes and for the determination of the effect of roentgen rays on the kidney. The subject was very adequately reviewed and investigated by Bolliger and Laidley. Their survey revealed a marked discrepancy in the results following the use of this experimental method. The cause of the variability, the authors suggest, resided in the fact that great differences existed in the methods employed by the various investigators. Furthermore, as will be seen later, the progressive nature of the lesions possibly led to confusion and misinterpretation. The following general conclusions as to the results obtained in the work prior to 1930 were offered by Bolliger and Laidley. Repeated doses of heavily filtered roentgen rays applied to the kidneys produce vascular lesions consisting of mural thickening and endarteritic changes in addition to alterations of tubular epithelium (degeneration, desquamation and cast formation). On the other hand, single doses of lightly filtered roentgen rays primarily induce tubular epithelial damage and subsequent abnormalities of the vascular tree and glomerular tufts.

The work of Bolliger and Laidley, because of its extensiveness, will be reviewed in some detail. The kidneys of young and middle-aged mongrel dogs were exposed to single large doses (3,870 roentgens in thirty minutes) of unfiltered roentgen rays after preliminary operative delivery of the kidney to the loin. Four groups of animals were studied. In the first group (A), one kidney was mobilized to the wound, irradiated and then replaced. The dogs of the second group (B) were first subjected to unilateral nephrectomy, and the remaining kidney was subsequently irradiated. A third group (C) and a fourth (D) were treated precisely as the first and second groups, respectively, except that the rays were applied for a shorter period of time.

In group A the treated kidney, except for early congestion and enlargement, was usually reduced in size. In group B the irradiated kidney was of normal size, perhaps as the result of compensatory hypertrophy consequent to unilateral nephrectomy. In group C there was an early increase in both size and weight with a reduction later, while in group D an increase in weight varying from 20 to 90 per cent was

observed. In all the groups the cortical surface was usually smooth in spite of severe contraction. When the other kidney was left in situ, marked fibrosis of the cortex was produced; when opposite nephrectomy was performed, uremia resulted within forty days after irradiation. Only occasionally was a granular surface found. The authors described five histologic stages (not sharply delimited from each other) which were present in all groups but less pronounced in groups C and D:

1. Acute congestion (up to forty-eight hours)—engorgement of glomerular capillaries, with enlargement of tufts, swelling of tubular epithelium and interstitial edema
2. Period of latency (from one to eight days)—no microscopic changes
3. Period of tubular change (from five to thirty-two days)—diminution of staining to loss of staining of cytoplasm, disappearance of nuclei, dilatation of convoluted tubules; edema of capsule, epithelial necrosis; proliferation of connective tissue and fatty degeneration of tubular epithelium; essentially normal conditions in glomeruli
4. Development of fibrous tissue (from twenty-one to sixty days)—progressive replacement fibrosis; very extensive fatty change in tubules except for rare hyalinization of tufts, normal conditions in glomeruli
5. Final period (from three to eight months)—marked thickening of capsule; in cortex, a few islands of hypertrophic tubules; except for tortuosity of vessels and occasional glomerular fibrosis, normal conditions in vascular units

Throughout there was a striking absence of inflammatory cells except for an early round cell infiltration.

Bolliger and Earlam dealt mainly with clinical observations in dogs in which the kidneys had been exposed to irradiation. The anatomic descriptions are corroborative of the results in the foregoing report. The authors claimed to have produced a rather constant lesion.

In 1931 Earlam and Bolliger determined the histologic changes which resulted from the application of one-half the dosage employed in the work of Bolliger and Laidley. Full grown dogs of various body weights were subjected to unfiltered roentgen rays of medium wavelength in a dose the equivalent of 1,900 roentgens. The lesions, in general, were similar to those reported after the larger doses of roentgen rays but were less intense and took longer to reach their maximum.

The anatomic result induced by a single massive dose (3,800 roentgens) of unfiltered roentgen rays was investigated by Earlam and Bolliger in 1932, and an attempt was also made to ascertain whether

the lesion resulting from application of a sublethal dose of roentgen rays was progressive. An irradiated kidney removed four hundred and seventy-seven days after treatment showed marked reduction in size and in width of the cortex. The glomeruli were small and atrophic, while those close to the surface were more or less completely fibrosed, with extensive hyaline changes. The tubules showed marked replacement fibrosis. The large vessels were tortuous; the smaller ones showed fatty change and thickening of the intima and hyalinization of the media. Another dog, similarly treated, from which the kidney was removed seventy-six days later, showed like but less pronounced abnormalities. Two dogs each received a sublethal dose of roentgen rays after unilateral nephrectomy. One killed at five hundred and thirty-four days showed changes similar to those shown by the dog that received the massive dose except that hyalinization was slight; the histologic preparations of the other animal, killed five hundred and nineteen days after irradiation, revealed scattered cortical scars, hyalinization of Bowman's capsule, tuft-capsule adhesions and atrophy of glomeruli—the latter "more especially when involved in a scarred area." The tubules peculiarly showed no changes. Clinical studies seemed to indicate that the last described lesion was not progressive, although such a statement does not seem conclusive.

Enger and Preuschoff reported their findings after applying repeated doses of roentgen rays to both kidneys in 4 dogs. Intervals of from eight days to three months were allowed to pass between applications. Anatomic observations were made at intervals of from four to sixteen months after the initial period of irradiation. Macroscopically there was renal contraction with a few medullary hemorrhages. Histologically the outstanding abnormality was degeneration of the tubular epithelium with infrequent areas of regeneration. Glomerular changes were not marked and consisted merely of occasional ischemia and hyalinization. The vascular abnormalities were insignificant except for rare reduplication of the elastic lamella and endarteritic changes. Interstitial fibrosis was also described.

A different approach in the study of the effect of irradiation on the kidney was pursued by Adams, Egloff and O'Hare. They gave repeated intravenous injections of active radium deposit to dogs. The earliest changes were hyalinization of glomerular capillaries and degeneration of the tubular epithelium. Those changes gradually became more pronounced and were accompanied by swelling of the basement membrane of the tubular epithelium, arteriolar sclerosis and interstitial fibrosis.

Two dogs received an injection of the active deposit directly into the renal artery. In one it produced renal contraction and histologic changes like those described. The other animal, however, revealed no notable changes. Animals which were permitted to die spontaneously in order to note the end-stage of the effects of the injection showed

advanced lesions of the type described previously, with diffuse replacement fibrosis. There was a 50 to 75 per cent decrease in the weight of the organs. Except for capillary hyalinization, the tufts were relatively well preserved. The viscera other than the kidneys generally showed no noteworthy changes, and the selective action on the kidney was attributed to the excretion of the radium deposit through the urinary tract.

Martinotti found hyperemia, swelling and granular degeneration of the convoluted tubular epithelium and no significant glomerular lesions in white rats. The kidneys of these animals had been exposed to unfiltered roentgen rays (from 200 to 100 kilovolts) or filtered rays (from 50 to 200 kilovolts). The nonirradiated kidney showed similar but less extensive changes. Notwithstanding these early changes in the nonirradiated kidneys, those of animals killed several months after treatment showed no abnormalities other than hypertrophy, while the irradiated organs were the seat of connective tissue proliferation. Irradiation of an area distant from the kidney with unfiltered rays produced degenerative epithelial changes only in the first portion of the convoluted tubules without any glomerular lesions, while examination several months later of a group of animals treated in this fashion showed no abnormalities. Irradiation of the kidney with soft rays, even up to 200 kilovolts, produced only transient epithelial changes and never fibrosis.

Page modified the experimental procedure of Bolliger and Laidley by applying roentgen rays to dogs' kidneys which had been transplanted subcutaneously. In some dogs one kidney was removed and the other transplanted, while in some the kidney was denervated.

The transplanted kidneys were subjected to repeated erythema doses of roentgen rays—from five to seven—for a period of from six to twenty-one weeks. The results of Bolliger and his associates were in the main confirmed. Page found "hyalin necrosis" of Henle's loops and epithelial proliferation to be the major and primary lesion. There were also proliferations of the interstitial connective tissue with concomitant vascular obliteration. Thickening and edema of the glomerular capillary wall were also observed but were less extensive than the changes in the tubular epithelium. The clinical findings in the treated group will not be discussed. Suffice it to say, the laboratory findings were similar to those found in man with chronic nephritis except that the animals showed hemoconcentration with rise of plasma proteins and plasma lipoids and an absence of anemia.

*Comment.*—The anatomic renal effects of irradiation are basically of two types, to repeat the summary of Bolliger and Laidley: Repeated doses of heavily filtered roentgen rays produce vascular lesions which consist of mural thickening and endarteritic changes in addition to

degeneration and desquamation of tubular epithelium and formation of casts. Single doses of lightly filtered roentgen rays primarily induce tubular epithelial damage with secondary development of vascular and glomerular abnormalities. Repeated intravenous injections of radium produce concomitant vascular and epithelial injury.

### LESIONS PRODUCED BY EXCESSIVE INGESTION OF PROTEIN OR IRRADIATED FOOD PRODUCTS

The production of renal damage in animals by overfeeding them with proteins is a matter of extreme interest, particularly in regard to its clinical application. This mode of experimental approach has been attended with many controversies and criticism, and the question of the relationship of excessive protein intake to Bright's disease, it can be said at the outset, is still far from settled. I shall include in this section, in addition to a review of the work on protein feeding, a discussion of attempts to produce renal lesions by dietary components in general.

Watson and his associates were the first to study the influence of a meat diet on the kidney and found that prolonged administration of such a diet (horse flesh) in rats produced renal hypertrophy. This was found even more pronounced in the second generation of animals. Histologic studies revealed severe granularity of the tubular cytoplasm, occasional nuclear pyknosis and karyorrhexis of various tubular segments. In the less affected rats only the ascending limb of Henle was involved. In the more severe conditions there were also casts and acute hyaline swelling of the glomerular capillary walls. These changes, however, were not observed uniformly throughout the series, while animals fed ox flesh showed less distinct changes.

Newburg fed rabbits a high protein diet. Animals that received egg white showed cloudy swelling and congestion (site not specified). Desquamation and vacuolation of the tubular epithelium and occasional dilatation of the tubules were also present. Another group received casein. One rabbit (found dead) showed hemorrhage into the lumens of some tubules and into an occasional subcapsular space. In others, there was evidence of "parenchymatous injury." A third group received soy beans (protein 37.8 per cent) exclusively. Microscopically there were tubular degeneration, cell desquamation and an interstitial increase with some round cell infiltration.

The results obtained are not conclusive. These experiments have been criticized because the diets were poorly balanced, especially in regard to vitamin content, and because some of the changes reported were noted in animals which were found dead. Tubular epithelium notoriously undergoes very rapid degeneration and autolysis after

death, so that the abnormalities noted might have been due to such a factor. Further, the tubular dilatation which the author stressed, has been known to occur spontaneously (see earlier section). The photomicrographs of the changes observed in the animals fed soy beans strikingly resemble those known to occur in spontaneous interstitial nephritis.

Drummond, Crowder and Hill restudied the problem of the relationship of diet to renal lesions. They were of the opinion that the tubular changes which Newburgh reported after excessive protein feeding were due to the deficiencies in vitamins. They consequently gave rats and kittens a diet rich in protein which contained, in addition, an adequate supply of salts and vitamins. Except for a diminished rate of growth the animals showed no abnormalities. The authors concluded that "the excretion of large amounts of nitrogenous waste products over considerable periods of time does not appear to cause damage to the kidneys in these species."

Shimizu, Nagawo and Machida repeated Newburgh's procedure in rabbits. Albuminuria and an increase in blood pressure were observed clinically, while microscopically there were capillary dilatation in the tufts and degenerative tubular changes.

Newburgh and Clarkson reinvestigated this question feeding groups of rabbits diets in which the protein content was 36 and 27 per cent, respectively. The cause of death in the rabbits of the first group (protein, 36 per cent) was undoubtedly inanition. Histologically there were dilatation of tubules with flattening of the epithelium and numerous casts (type?). In the second group (protein, 27 per cent) there were renal hypertrophy, cloudy swelling of the epithelium of the convoluted tubules, desquamation and vacuolation. These changes also occurred in stock animals but less diffusely. There was no true glomerulitis. Only 1 of 13 controls showed a similar diffuse pathologic change. It was felt that the diet might produce the lesion either through the excretion of amino-acid or as the result in part of the acidity of the urine. These experiments are open to the criticism that was directed toward the previous work and cannot, therefore, be considered conclusive. Urinary changes such as were reported in these animals (albuminuria, cylindruria) were not observed by Addis.

In order to overcome this criticism, Polvogt, McCollum and Simmonds, like Drummond, gave rats diets high in protein (from 31 to 41 per cent) which contained also adequate inorganic elements and vitamins. The kidneys of animals killed and examined four hundred days after the beginning of the experiment were enlarged and congested and showed tubular degeneration and dilatation with cellular desquamation and hyaline casts. The controls showed none of these changes. The abnormalities were attributed to excessive excretion of the end-

products of protein metabolism. Although this is undeniably a factor, Donaldson in his exhaustive studies on the rat showed that the weight of the kidney increased proportionately with that of the body. That the enlargement is attributable to the experimental diet alone is therefore doubted. The work of Polvogt and his co-workers, however, indicates that renal hypertrophy may result from excessive protein feeding—a point subsequently confirmed.

The observations of Osborne, Mendel, Park and Darrow and of Osborne and Mendel were somewhat at variance with the findings of Polvogt. Osborne and his co-workers fed rats with high protein diets which were also adequate in vitamins A and B and inorganic salts. These animals grew well. At autopsy the kidneys, although distinctly hypertrophied, histologically showed no evidence of either inflammatory or degenerative changes.

Evans and Risley fed white rats high protein diets to which greens were added for vitamin content. In their series 69 per cent of the tubules were claimed to show epithelial degeneration, and 46 per cent of the glomeruli, fibrosis, enlargement and exudate (?). Some showed an interstitial collection of round cells and thickening of Bowman's capsule. The controls showed no abnormalities. The diet used invites the same criticism that was applied to Newburgh's, namely, lack of vitamins. The microscopic descriptions were not complete, and the accompanying photomicrographs lent no support to the conclusions of these authors that "animals fed on the high protein ration for prolonged periods showed nephritic changes without exception." Addis in his discussion of the paper reemphasized the disagreement in results as reported by different investigators and felt "that the question as to whether a high protein intake produces renal damage is still unanswered."

Miller in his study of the effect of high protein feeding in rats (diets contained from 1.36 to 40.13 per cent protein) reported only enlargement of the kidneys, of the glomerular tufts and of the diameters of the convoluted tubules. Microscopically there was no evidence of any nephritic process. He quoted the conclusions of Howe, who fed monkeys (ordinarily they do not tolerate more than 8 per cent protein) a diet containing from 18 to 25 per cent protein without production of nephritic changes.

The investigation of Reader and Drummond is important so far as it bears directly on the tubular changes previously reported by Newburgh and his co-workers as due to protein excess. Reader and Drummond fed rats diets which contained from 45 to 90 per cent protein. Renal enlargement and slight degenerative changes were present in both the control and the experimental group, and it was felt therefore that such abnormalities could not be ascribed to the experimental method. These workers concluded that "excretion of relatively very large

amounts of nitrogen over periods of four months does not appear to damage the kidneys of rats." Kennedy came to a similar conclusion. Hypertrophy of the kidney alone, unaccompanied by histologic changes, was reported by Addis, MacKay and MacKay to have occurred in rats which were fed diets containing 70 per cent protein.

Similar observations were made by Jackson and Riggs, who administered diets very rich in protein (78 per cent) to rats for periods of from ten to twenty months. They noted hypertrophy of the kidneys but no histologic renal changes. They further stressed the important fact that albuminuria, previously reported as clinical evidence of experimental renal abnormality, was a normal finding in the rat.

Smith and Moise after unilateral renal extirpation in white rats found an increase in hypertrophy of the remaining kidney which was directly proportional to the protein content of the food. Determinations of the total solids of the organ showed that the enlargement was due to an actual increase in tissue. Hypertrophy of the remaining kidney after extirpation of its fellow is well known clinically and experimentally and is attributed to a compensatory mechanism. The enlargement has been shown to be due to actual hypertrophy and hyperplasia of the glomerular units and of the tubular epithelium (Matsuyama, Oliver, Arataki). Arataki further showed that actual proliferation of the interstitial connective tissue was a factor in the production of the enlargement. The contribution of Moise and Smith lies in the fact that they showed an increase which paralleled the protein content.

Jackson and Moore repeated the experiments of Smith and Moise. White rats in which one kidney had been removed were given a diet which consisted of 76 per cent casein for from two to seventeen months. The average hypertrophy of the remaining kidney was 136 per cent. In some the glomeruli showed tuft enlargement. In others, there was partial to complete replacement fibrosis of the glomerular tufts with occasional hyalinization and glomerular adhesions. The tubules were dilated; their lining epithelium was flattened and showed occasional cellular regeneration. The authors remarked that the more pronounced lesions were seen in the older animals. The tubular injury was believed to be primary. That the fibrosis might be entirely the result of spontaneous disease cannot be denied.

Work similar to that of Newburgh and his associates was undertaken by Ishiyama, who fed rabbits a mixture of soy beans and a vegetable-protein combination. Histologic studies of the kidneys were reported to show enlargement and hyperemia of the glomerular tufts, contraction of the injured tubules (?) and increase of the interstitial connective tissue.

More recently Krylow reported enlargement of the kidney with hypertrophy of the tufts, cellular hyperplasia (probably of the endo-

thelial type—also seen in control animals), degeneration of capillary walls and proliferation of capsular epithelium in frogs which had been given a high protein and fat diet. The tubular epithelium in scattered portions was the seat of cloudy swelling and fatty change. The tubular lumens were often widened, and there were frequent inflammatory (polymorphonuclears) foci and parasitic cysts in the interstitium. He also reported acceleration and exaggeration of the pathologic processes ("glomerulonephritis" and "glomerulonephrosis") after the administration of sodium chloride.

Spies and Glover reopened another approach to the production of renal lesions. They administered large doses of viosterol to rabbits. Cachexia, anorexia and diarrhea, albuminuria and oliguria were often seen clinically. Histologic studies of the kidneys showed sclerosis of scattered interlobular arteries and vasa afferentia with subendothelial deposits of hyalin and diminution of the lumens. Fused masses of necrotic material, calcium, cellular débris and occasional leukocytes were found. The internal elastic lamella of the venae interlobulares was thickened and fragmented. The tubules showed thickening of the basement membrane and hyalin between it and the epithelium. The glomerular basement membrane was thickened, hyalinized and calcified. Abundant deposition of calcium was found in hyalinized foci. The control animals showed no changes.

Similar observations have been made by other investigators. The agent most frequently employed to produce such changes has been viosterol. Parathyroid extract has also been employed, and occasionally calcium itself. The following groups of experiments are all of a similar nature and largely confirmatory one of the other.

Hueper produced calcification of all organs and more particularly of the kidneys of dogs by injecting large doses of parathyroid extract. The various structural units of the kidney were the seat of calcareous deposits. Occasionally the renal changes were so severe as to produce clinical evidence of renal insufficiency.

Following the feeding of rats, cats and mice with large doses of ergosterol, Kreitmair and Hintzelmann described calcification within the glomeruli and occasionally within the walls of the vasa afferentia. Calcium casts were also noted in the lumens of the straight tubules.

Reyher and Walkhoff found "toxic nephrosis" (epithelial degeneration, desquamation and calcium cast formation) in mice and rats which were given irradiated foodstuffs.

Kreitmair and Moll reported calcification of the renal arteries in addition to involvement of the arteries in general in rats, cats, mice and dogs which were given viosterol.

Rabl investigated the pathologic changes induced in mice after excessive doses of viosterol. In the group that received viosterol alone there

were calcification of tubular basement membranes and some epithelial calcium inclusions. Here and there, calcification of the arterial wall and an infrequent calcareous cast were found. Another group received viosterol in combination with sodium phosphate and revealed massive calcium casts and epithelial deposits in the tubules. A third group received viosterol and calcium carbonate. The changes were similar to those in the second group. A group receiving sodium phosphate alone showed no changes. Where calcium deposits were found in the kidney they were also present in other viscera.

Smith and Elvove gave full grown rabbits viosterol in almond oil. Calcium deposits were found within the convoluted tubules, casts in the lumens of the straight tubules and associated "acute or chronic diffuse nephritis."

Holtz and Brand administered viosterol to rats and described calcification of the arterioles. There were also occasional deposits within the glomerular capsule and the tubular epithelium.

Hückel and Wenzel attempted to produce renal lesions in rabbits with excessive doses of viosterol. They obtained lesions consisting of vascular medial calcification, foci of medial necrosis and cellular proliferation. Occasional cellular proliferation of the intima with some encroachment on the lumen was found. The tubules showed calcification with calcareous cast formation, and there were rare calcium deposits within the capsular epithelium and the glomerular tuft itself.

Learner repeated the work of Hueper in dogs and mice. In dogs Hueper's observations were confirmed. In mice, however, there were no calcareous deposits except within the bronchial cartilages.

Kraus reported diffuse glomerular enlargement and cellular hyperplasia with an increased number of leukocytes in the tufts, occasional crescents and degenerative tubular changes in 1 of 3 rabbits which had received garlic extract in combination with viosterol and cholesterol. Two other animals which received garlic extract alone showed no changes. The glomerulonephritis was ascribed by Kraus to the extract plus a peculiar individual susceptibility. Such an explanation, however, does not appear acceptable. The changes described undoubtedly represent a spontaneous disease.

In a rabbit that had been given repeated doses of viosterol, Billig described changes similar to those observed by Hückel and Wenzel. The glomerular changes were of a somewhat different nature. Their erythrocytic content varied, and foci of cloudy swelling, necrosis with leukocytes and tuft enlargement were also observed. In some of the necrotic foci bits of calcium were deposited. The necrosis was usually found at the hilus of the tuft. Billig thought that these were inflammatory foci and due to direct injury. The possibility that these lesions were the result of vascular narrowing must be entertained, however.

Cramer, working on rats, found that omission of magnesium salts from the diet would produce lesions of the kidneys. Grossly, the kidneys were often enlarged and the surfaces scarred. Histologically, the tubules showed degenerative changes, and there were occasional glomerular and tubular deposits of calcium. Approximately one half of the controls, however, also showed degenerative changes of the tubules with calcification at the corticomedullary junction. This change was attributed to the vitamin D in the cod liver oil and did not occur in the controls when butter was substituted for the cod liver oil. In this series the calcareous deposits and degenerative changes were observed only in the animals which had been given a diet free from magnesium salts.

The toxicity of viosterol in rats was further studied by Duguid, Duggan and Gough, who reported two varieties of renal lesions: calcification of the renal arterioles (as part of a general arterial involvement) and formation of calcium casts in the tubules. They showed that a diet free from vitamins and rich in phosphate and calcium contributed to the toxicity which viosterol had for rats. Calcareous casts in the tubules and marked calcification of the renal arterioles were described. The latter was considered to be a good criterion of the toxicity of viosterol, while the former occurred too frequently in rats to be used as a reliable index.

The relationship of overdoses of vitamin D to renal changes was studied by Gough, Duguid and Davies. They combined the vitamin D with sodium phosphate. The effect of sodium phosphate alone on the kidney had been noted by Hirsch, who injected a 20 per cent solution of monobasic sodium phosphate into rabbits subcutaneously and observed necrosis of the tubular epithelium, which was most severe in the convoluted tubules and less marked in Henle's loops. Similar lesions had been reported in rats and rabbits by Harris and Innes after feeding them with a high phosphate diet. They also had showed that an increase in the calcium content of the diet exaggerated the hypervitaminosis and produced deposition of calcium. Gough and his co-workers gave young rats bread and potato to which acid sodium phosphate was added in one group and trisodium phosphate in another group. Some of the rats of each group were given in addition large amounts of vitamin D. Nephrosis was most pronounced in the animals which received acid sodium phosphate and excessive doses of vitamin D (extensive necrosis and desquamation, collapse and occasional disappearance of groups of tubules). Calcification, however, was also marked and seemed to go parallel with the renal excretion of these substances. In the other control animals similar but not especially significant tubular changes were present. In animals given alkaline phosphates, there was

an increased tendency to calcification alone. The authors believed that vitamin D exaggerated the toxic effect of the acid sodium phosphate.

Following Hirsch and Harris and Innes, MacKay and Oliver administered a diet which contained an excess of inorganic phosphate (acid, basic or neutral sodium or potassium phosphate) to female albino rats for a period of forty-four days. The diets were adequate and varied only in their phosphate content. At necropsy the kidneys were usually gray-white and occasionally granular. Histologically, the tubules in the outer medullary zones were lined by atypical hyperplastic regenerated epithelial giant cells with oval vesicular nuclei. Many lumens were filled with débris and calcareous masses. Occasional perivascular round cells and fibrosis were found. The cortex was believed to be secondarily involved, with cystic dilatation and occasional collapse of the tubules.

The earliest lesion was necrosis of the terminal portions of the proximal convoluted tubules, then extension, regeneration and deposition of calcium salts and interstitial fibrosis. The glomeruli remained unchanged. This conclusion was largely confirmatory of the report of Hirsch.

Duguid reported the results of studies in which rats were given large amounts of orthophosphates in conjunction with overdoses of vitamin D. The primary lesion was parenchymatous degeneration with focal calcification of the tubules, secondary replacement fibrosis and atrophy or dilatation. Glomerular changes were secondary and consisted of hyalinization and thickening of the capillary membranes, disappearance of endothelial cells and obliteration of arterioles. The arteries were narrow and tortuous and showed reduplication of the internal elastic lamina. An interesting incidental finding in rats which were alive two or more months after treatment began was cardiac enlargement. The author felt that the cardiac hypertrophy was not due to arterial disease but was the result rather of myofibrillar degeneration.

*Comment.*—The observations on the effect of excessive feeding of protein and irradiated food on the development of lesions in the kidneys are of undoubted interest. A definite opinion as to the nature of the renal changes after such feeding of protein is, however, not tenable. Although tubular lesions may occur, the bulk of the experimental evidence seems to indicate that the degenerative alterations following such a regimen are minimal, and that the only anatomic result is a work-hypertrophy of the kidney consequent to the increased excretion of protein.

The major value of the other experimental procedures discussed in this section resides in the lucid demonstration that large doses of irra-

diated products, calcium and phosphates have a distinctly harmful effect on the living organism (through injury to the mesenchymal tissues—Hübschmann).

These experimental studies assume greater significance when considered in the light of recent reports by Albright and Bloomberg, who have reemphasized the relationship and clinical importance of hypercalcemia and hypophosphatemia in human pathology, with particular reference to the abnormalities produced in the kidney in these conditions.

### LESIONS PRODUCED BY BACTERIA AND BACTERIAL TOXINS

Bacteria and their toxins have long been accused of having an etiologic relationship to glomerulonephritis. Often the disease has followed acute tonsillitis or other pyogenic infection. The frequent association of infections with Bright's disease has been stressed by Longcope and his co-workers, who demonstrated the presence of an infection (tonsillitis, sinusitis, bronchopneumonia and scarlatina) in 85 per cent of their 40 cases of acute diffuse glomerulonephritis. Cultures from the foci of infection in 32 of these cases showed hemolytic streptococci of the beta type in 68.7 per cent and streptococci of the alpha type in 12.2 per cent. Persistence of the infection was demonstrable in 10 of the 12 cases that were observed to the development of chronic diffuse glomerulonephritis, although cultures of the blood and urine were uniformly negative.

There are still much discussion and indecision as to whether or not bacteria are directly responsible for the initiation of the disease process. The possibility has been suggested that the development of allergy or hyperergy is the important factor in the onset and course of nephritis in man. It is well known, for example, since the time it was first emphasized by Escherich and Schick that typical diffuse glomerulonephritis does not usually occur in scarlatina until the third week of the disease. Schick showed that the period of incubation of scarlatinal glomerulonephritis may be linked with that of the formation of antibody and that the lesion in the kidney is an allergic response to the virus of scarlet fever. Escherich and Schick contended that the virus of scarlatina circulates in the body during the acute stages of the disease, sensitizing the cells. A subsequent reactivation of an infected focus results in an antigen-antibody reaction, the disease appearing then after a period of latency. Pearce in 1910 believed that the lesions of glomerulonephritis in general were due to long-continued action of toxic substances, and that since the glomeruli are the sites of elimination of such substances the changes represent the response of the capillary walls to the long-standing action of the toxins. Schridde offered the opinion that Bright's disease is due to the action of the

products of bacterial growth, toxins manufactured at a point other than the kidney, and that it is not due to a direct effect of bacteria locally. Ophüls believed that the endothelium of the glomerular tufts acquires bacteriolytic power during active infection. On reentrance of bacteria after a period of quiescence, an explosive reaction is produced which destroys bacteria and leads to the production of lesions.

That an allergic mechanism is involved seems to be borne out further by the fact that the diffuse glomerulonephritis associated with subacute bacterial endocarditis is most often an accompaniment not of the active bacterial disease but rather of the bacteria-free (healed or healing) stage. Harbitz and also Libman were the first to call attention to this interesting fact. Subsequent studies were made by Baehr and Lande. Baehr in 1931 stated, "The rarity with which glomerulonephritis was observed in the patients with persistent bacteremia proves that the mere presence of the streptococcus in the blood stream is not the immediate cause of glomerulonephritis. Its far greater frequency in the bacteria-free cases (33.3%) must therefore have some relationship to phenomena concerned in or following the killing off of the bacteria." Moreover, although diffuse glomerulonephritis occurs often enough during the course of an infection, it is more commonly observed during the apparent decline of an infection. Friedemann and Deicher, on the basis of Schick's view, associated a streptococcic agent with the disease. They felt that one effect of antibacterial antibodies on streptococci is the liberation of endotoxins which can produce nephritis. Antiendotoxins capable of neutralizing endotoxins, however, appeared as one of the antibacterial antibodies. When endotoxins appeared earlier or in greater abundance than the antiendotoxins, nephritis was the result. Thus in scarlatina they believed that streptococci remain in various foci after the subsidence of the acute infection. Toward the end of the third week antibacterial antibodies appear against streptococci, which combine with these and then produce toxic products (endotoxins) which in turn result in renal changes.

The hemolytic group of streptococci—perhaps the toxic product of their growth, as indicated in the foregoing statements—has been frequently implicated as the etiologic factor. It is interesting in this regard to note that Trask and Blake demonstrated the presence of a toxic substance in the blood serum and urine of patients with scarlet fever and on this evidence based their belief that scarlet fever is merely a local inflammation of the throat due to members of the hemolytic group of streptococci and that the general features of the disease are caused by the liberation of toxins. Of interest, also, in this connection are the observations of Hansen and his co-workers, who studied the skin reac-

tions to filtrates of cultures of the hemolytic streptococcus in patients with acute tonsillitis and glomerulonephritis. Although a fair proportion of the controls exhibited positive skin reactions, the more distinctive reactions were observed in the patients with tonsillitis and nephritis, with particularly strong reactions in the latter. The observers concluded that the "development of a diffuse glomerulonephritis in patients suffering from hemolytic streptococci infections may be referable to the products of growth of these organisms acting upon previously sensitized kidney cells."

Clinical observations of the apparent relationship of infection to renal disease have suggested the use of bacteria and their products experimentally in the study of glomerulonephritis. The arrangement of this section has been rendered difficult because of the inevitable overlapping of the methods which are concerned with direct and indirect approaches to the problem.

Bell, Clawson and Hartzell injected streptococci obtained from human sources into rabbits and young monkeys (Macacus rhesus) intravenously every few days until the appearance of moderate albuminuria. The renal lesions observed in the rabbits were of the spontaneous type. In 5 of the 14 monkeys significant renal changes developed. Two of the animals showed extensive tubular necrosis, tubular hemorrhage and occasional necrosis of the glomerular tufts. One monkey showed "acute interstitial nephritis" similar to the spontaneous lesion except for its slightly wider distribution. One monkey showed evidence of glomerulonephritis, but this appeared to be of a focal type. In this animal, also, the larger medullary arteries presented foci of suppuration associated with aneurysmal dilatation. In 5 to 10 per cent of the glomeruli hyperplasia of the capsular epithelium was noted. There were, in addition, hypertrophy of the capillary endothelium and tuft fusion, while an occasional tuft revealed large numbers of polymorphonuclear leukocytes.

In a series of papers Duval and Hibbard reported the results of their studies of the effect on rabbits and dogs of injections of streptococcic lysate. The rabbits received intravenous, intraperitoneal or subcutaneous injections of a culture of Streptococcus scarlatinae. The immunized animals were then given intraperitoneal inoculations of the living culture. The intraperitoneal fluid of these animals was subsequently collected, filtered and injected intravenously into normal rabbits. Only the more significant anatomic effects in the kidney were reported, although other viscera revealed congestion, edema and parenchymatous degeneration. The kidneys were usually enlarged; the cortical surfaces were peppered with punctate hemorrhages. Necrosis, hyperemia and capillary thrombosis were found within the glomerular tufts. Crescent

formation was also described. The tubular epithelium was often desquamated, and there were casts. The photomicrographs appear to represent lesions of the focal type.

Subsequently Duval and Hibbard again employed streptococcic lysate and obtained degenerative visceral changes. Beside using the filtered peritoneal lysate, they treated cultures of the streptococcus in vitro with activated homologous immune serum. The cultures were then filtered, and the filtrate was employed in the same way as the peritoneal lysate, with the production of lesions similar to those previously described. The authors concluded that the toxic factor of Str. scarlatinae is bound with the protoplasm of the cell and that the renal change is due to protein intoxication. In an immune animal, it was believed, the introduction of a living homologous bacterial culture produces acute glomerulonephritis owing to the presence of an agent which splits the bacteria to form an endotoxin, which then effects renal damage. In a normal animal, on the other hand, the "lysate" being the toxic product of the organism, no previous lytic action is required to produce the renal lesions.

The production of renal changes in young dogs by intravenous and intraperitoneal injections of "toxins" was reported by Duval in 1931. He employed live cultures (the forty-eight hour surface growth of three blood agar slants, suspended in water), killed cultures (the entire forty-eight hour surface growth of blood agar slants, suspended in saline solution) and "lysate" (prepared in an immune rabbit).

The injected live cultures produced enlargement of the kidney and occasionally punctate hemorrhages in the early stages, while kidneys examined later were slightly reduced in size and scarred. Microscopically, there were engorgement of glomerular capillaries and red cell thrombi. An occasional hemorrhage into the subcapsular space with fibrosis of loops and formation of crescents was seen, while the tubules showed late degenerative changes and a variety of casts. The interstitial changes were most severe and consisted of focal and diffuse lymphocytic collections and bacteria. With the use of the lysate or a killed culture, the glomerular endothelium was primarily affected, with formation of capillary thrombi. Six months after repeated injections of the lysate there were interstitial repair with secondary glomerular and tubular atrophy and occasional necrosis. The killed cultures of the streptococcus produced glomerular capillary lesions with thrombosis and fusion to Bowman's capsule and endothelial proliferation. The renal changes were reported to have always been intensified by a second injection.

Reith, Warfield and Enzer attempted to reproduce the results of Duval and his co-workers but could neither prepare a sterile peritoneal bacteriolysate nor obtain lesions which resembled scarlatinal nephritis

as claimed by Duval and Hibbard. They encountered renal alterations similar to those described by Duval and his associates in normal rabbits and in animals that had received injections of bacterial suspensions other than that of scarlatinal streptococci.

Dake investigated the effect of various toxins on the kidneys of rabbits and guinea-pigs. Single injections of diphtheria toxin produced macroscopic hyperemia. Histologically there were swelling and engorgement of scattered glomerular loops as well as swelling and degeneration of the capillary walls and the attached cells. Occasional "cyst" formation with rupture of the capillary wall and hemorrhage was also found. The capsular spaces contained desquamated epithelial cells, leukocytes and erythrocytes and, here and there, a periglomerular exudate of round cells and "pseudo-eosinophilic" leukocytes. The tubular epithelium showed degenerative changes which varied from cloudy swelling to necrosis with frequent nuclear pyknosis and karyorrhexis. The interstitial tissue contained scattered cellular infiltration, and there was swelling of the endothelial cells of the intertubular capillaries. Dake believed that anaphylaxis played an important rôle in the production of lesions by diphtheria toxin, for severe albuminuria appeared in animals which had been previously sensitized. Histologic preparations of this particular experimental group were not made.

Following single intravenous injections of a filtrate of a culture of Bacillus paratyphosus B into rabbits, regressive changes appeared in the cells of the glomerular tufts, with occasional cell proliferation. The tubular epithelium showed cloudy swelling, hyaline droplet formation, cellular desquamation and nuclear pyknosis. Animals sensitized with the toxin of B. paratyphosus B and given bacilli subsequently showed no additional features, so that Dake concluded that allergy was not concerned in the development of lesions in this group.

Single intravenous doses of a filtrate of a culture of Bacillus typhosus produced but slight regressive changes, only occasionally a cellular proliferation of scattered tufts and infrequently erythrocytes and leukocytes within Bowman's spaces. The epithelium of the tubules showed cloudy swelling and hyaline droplets. Here, too, the author felt that immunity played no rôle.

Pneumococcus toxin and pneumococci injected intravenously in single doses produced slight swelling of the cells of the glomerular tufts. Occasional collections of cellular débris and erythrocytes within Bowman's spaces and degenerative tubular epithelial changes with erythrocytes within the tubular lumens were also found. Previously sensitized animals showed more pronounced abnormalities. Injections of a filtrate of a culture of Staphylococcus aureus produced only cloudy swelling of the tubular epithelium.

Clawson gave rabbits repeated intracardiac injections of a live culture of Streptococcus viridans (obtained from patients with acute rheumatic fever). The bacterial suspensions were injected with ground agar. Infarcts of the kidney were produced in 50 per cent of the animals (14 rabbits). Microscopically, there were exudation of polymorphonuclears either in a portion or throughout the entire tuft, occasional endothelial cell proliferation and infrequent crescent formation. The percentage of involved glomerular tufts varied from 4 to 45. In rabbits given injections of streptococci agglutinated by a specific serum the glomerular injury was decidedly less extensive and less severe. The lesions were all of the focal embolic type.

Large amounts of a hemolytic culture of Staph. aureus were repeatedly inoculated by Domagk and Neuhaus at intervals of from several days to weeks. Injections were made by means of a metal catheter which had been introduced through the femoral artery and into the descending aorta to the level of the origin of the renal arteries. Some of the animals studied had been previously sensitized. After a single injection the authors found endothelial swelling and phagocytosis. After repeated injections, the glomeruli showed ischemia, cellular proliferation and occasionally crescent formation. An increase in leukocytes was observed only for a short period after injections and was also seen in the tubules and interstitial tissue. After treatment had been prolonged for several weeks the process became more diffuse, with both acute and organizing glomerular lesions coexisting side by side. In this stage leukocytes were not found. The tubules, mainly the convoluted, showed hyaline droplet degeneration, while the lumens contained occasional erythrocytes and hyaline casts. Infrequent renal infarcts were present. The photographs and descriptions seem to correspond to focal glomerulitis.

Gray carried out a series of experimental procedures in addition to making a partial survey of the literature. His work on the effect of chemical poisons on the kidney has been mentioned in the section dealing with that subject. He also administered single and repeated injections of diphtheritic and streptococcic toxins and studied the renal injuries produced in rabbits and rats. Abnormalities were obtained after both single and repeated injections. The relative effectiveness of single and repeated injections in the production of lesions was not indicated. The main alterations were noted in the glomerular tufts, with less distinct abnormalities in the tubular units. In the former, swelling of cells, karyorrhexis, round cell infiltration and necrosis, with occasional blood cyst formations, were reported; in the latter, fatty change. The changes were believed to be due to the "colloidal nature" of the toxins and "lack of filterability through the glomerular membranes with exaggeration of action due to the local concentration." Intravenous injections of bacteria

(hemolytic and nonhemolytic streptococci, Morgan's bacillus and staphylococci) produced variable changes, including glomerular congestion, cellular infiltration and endothelial and capsular epithelial degeneration. The focal distribution of the lesions was attributed to the fact that all glomeruli did not function simultaneously.

Important contributions to the study of experimental renal lesions were made by Shwartzman, Apitz and Gerber. In 1928 Shwartzman called attention to a new immunologic phenomenon, since referred to by his name, that of local skin reactivity to bacterial filtrates, as follows:

> If a potent bacterial filtrate free from autolytic products is injected into the skin of a rabbit ("skin preparatory factor"), no appreciable reaction results. The strongest effect obtained is a moderate erythema which promptly subsides. However, if 24 hours after injection the rabbit is injected intravenously ("reacting factors") with the same or another potent bacterial filtrate, 4-5 hours after the intravenous injection there appears an extremely severe hemorrhagic necrosis at the site of injection—*the sine qua non feature of the phenomenon is that the second injection be given via the blood stream.*

Since then the phenomenon has been elicited not only in the skin but also in other organs (Shwartzman).

Shwartzman and Baehr in 1928 injected directly into the left renal artery of the rabbit after clamping the corresponding vein a filtrate of a culture of B. typhosus. Five minutes after the injection was executed the clamp was released. Later the right kidney was given an injection of phenolized saline solution. Twenty-four hours after this a filtrate of a culture of the same organism was introduced into the aural vein. Twenty-four hours after the last injection the left kidney showed pronounced hemorrhagic and necrotic lesions. On the basis of this experiment, carried out in a series of rabbits, Shwartzman felt that preparatory factors could induce in the kidney a state of reactivity by way of the vascular system, possibly owing to the high permeability of the vessels. In other organs, e. g., the ear, a similar response could be obtained only when an additional agent such as testicular extract or thermal hyperemia was combined with the injection of the filtrate (Shwartzman, 1935).

Gratia and Linz, and Apitz studied the relationship of the Shwartzman phenomenon to the production of general visceral lesions with a filtrate of a culture of Bacillus coli. All the injections were given by the intravenous route. Apitz found that a single injection of such a filtrate produced general nonspecific effects such as hepatic necrosis, pulmonary edema, hydropic swelling of the liver cells, myocardial degeneration and hemorrhagic inflammation of the subcutaneous tissues. After a single injection, renal lesions except for some cloudy swelling were insignificant. After repeated injections (twenty-four hours apart), on the other hand, the anatomic results were much more severe and extensive, particularly in the kidneys. The kidneys showed cortical

necrosis, hemorrhage into the glomeruli, fibrinous thrombi in capillary loops and regressive changes with disappearance of nuclei. There were also necrosis and fibrinous thrombosis of the arteries, infarction, fatty degeneration and necrosis of tubular epithelium. The other viscera presented hemorrhages, occasional fibrinous thrombi of vessels and inflammatory infiltrations. Apitz obtained the renal lesions only after two intravenous injections with one exception, that of a pregnant animal in which a single dose produced similar lesions. Although morphologic evidences of damage could not be demonstrated, he expressed the opinion that a preparatory intravenous dose of bacterial filtrate or possibly pregnancy alters the vascular endothelium—a change which is expressed in a state of altered reactivity.

The results of Apitz were confirmed by Gerber, who employed filtrates of cultures of the meningococcus and the typhoid bacillus. Gerber also emphasized the occurrence of venous thrombi in the absence of any demonstrable endothelial changes. Here, too, the general visceral degeneration and venous thrombi were obtained with either one or two injections of bacterial filtrate, while renal changes were elicited only with two intravenous injections given twenty-four hours apart.

Rich, Bumstead and Frobischer, on the basis of their belief that the renal changes associated with bacterial endocarditis were due to the action of toxins rather than emboli, inoculated rabbits intravenously with a bacteria-free filtrate of Str. viridans (isolated from a case of subacute bacterial endocarditis). The animals were put to death on the day following injection. Hemorrhages into the glomerular subcapsular spaces and tubular lumens were found in 29 per cent of 79 animals. Rich and his associates could not produce renal changes with other bacterial filtrates.

In the course of his studies on the pathogenesis of inflammatory lesions of the joints, Pescatori described incidental lesions similar to those obtained by Dake, in animals which had received an intra-articular inoculation of diphtheria bacilli. There were hemorrhage within tufts and exudate in Bowman's space, degenerative tubular changes, hyaline and granular casts, and occasional thrombus formation in the glomerular capillaries.

Hückel in 1930 injected Dick toxin into the renal vein (directed toward the kidney) and obtained capillary hyperemia and polynucleosis of the glomerular tufts. That the polynucleosis of the tuft was not due to generalized leukocytosis was shown by the paucity of leukocytes in the other renal vessels. There also were endothelial proliferation, swelling of capsular epithelium and edema of the capsule. These changes were claimed to be diffuse. Two of his rabbits received repeated doses of toxin intravenously (aural vein). One showed no significant alterations.

The changes in the other attributed to this procedure were probably those of spontaneous interstitial nephritis, or they represented, perhaps, a reactivation of mesenchyme, as pointed out by Vaubel, Masugi and Ahlström (see later paragraphs).

In 1935 he stated that in the further course of these lesions he did not see a picture typical of human glomerulonephritis but only evidence of interstitial inflammation.

In 1931 Hückel again investigated the effect of subcutaneous or intravenous injections of Dick toxin and streptococcic filtrate on the rabbit's kidney. Following each of these, degenerative epithelial changes appeared within the tufts with desquamation into the capsular spaces. Ischemia of the tufts, swelling and vacuolation of the glomerular epithelial cells, and enlargement and increase in number of the endothelial cells were also encountered, with interstitial foci of lymphocytes and scattered oxidase-positive cells. The tubular epithelium showed degenerative changes.

The results of an interesting study were presented by Kô, who injected various strains of hemolytic streptococci into the palatine tonsils of dogs. In another series the organisms were injected intravenously, in single doses. Albuminuria was observed clinically in the infected animals, usually four days after inoculation. Histologic preparations of animals in which the tonsils had received injections showed hyperemia, cellular proliferation of the glomerular tufts, albuminous exudate and occasionally red blood cells within the capsular spaces, swelling of the capsular epithelium, hyaline casts and an interstitial cellular infiltration. Intravenous injection, peculiarly, was found to be less effective in producing nephropathy. The lesions described in both groups, however, were focal.

The allergic response to bacterial infection was stressed by Lukens and Longcope. These investigators used two strains of hemolytic streptococci, one of which was obtained from the inflamed tonsils of a patient with acute diffuse glomerulonephritis. They employed 52 rabbits, 23 of which were "sensitized" by an additional intradermal injection of from 0.2 to 0.5 cc. of a heavy suspension of living hemolytic streptococci. The sensitized group and a control group of 29 normal animals then received killed bacterial cultures directly into the renal artery. Renal lesions were observed in only one-half the animals. The abnormalities appeared within eight hours after intra-arterial injection, tended to reach their acme within five days and then seemed to recede. The glomerular tufts showed hyaline capillary thrombi, necrosis, exudation of polymorphonuclears and later round cells. Occasional crescents were also found. The tubular epithelium was swollen, and the lumens contained hyaline casts. Red blood cells were seen but rarely. These

lesions were focal in distribution, occurred in both the sensitized and the control group and were distinctly of the so-called embolic type. Nephropathy, however, was reported as decidedly more common in the sensitized animals—in the ratio of 73.9 to 27.5 per cent. On this basis the authors felt that the glomerulitis obtained was possibly dependent on an allergic state in the affected kidney.

In a subsequent study Lukens injected a heated suspension of hemolytic streptococci into the renal artery of the rabbit at intervals of seven days. Three rabbits which were examined four days after the third injection showed endothelial swelling and desquamation in the kidneys, occasional hyaline thrombi in the capillaries of glomerular tufts, infrequent hemorrhages into the subcapsular spaces and epithelial crescents. There was also interstitial infiltration by mononuclear cells. Organisms could not be demonstrated. Several vessels (type?) were thrombosed and were associated with renal infarcts. The kidneys of other rabbits examined after one and two repeated intra-arterial injections showed no significant changes. The author believed the changes to be due to a phenomenon analogous to the Arthus phenomenon.

McLeod and Finney, working along the lines of Lukens and Longcope, inoculated rabbits with cultures of Str. viridans isolated from the throats of patients with glomerulonephritis or rheumatic fever. Of the 57 rabbits used in the experiment, 24 were normal, while 33 were sensitized by a procedure similar to that of Lukens and Longcope (see foregoing paragraph). After this sensitization, a heavy heated bacterial vaccine was injected into one renal artery of each animal. Renal lesions were noted in 19 (33.3 per cent) of the 57 animals (16.6 per cent of the normal animals and 45.1 per cent of the sensitized group) and although rather widespread were of the focal variety.

Skin tests were carried out to determine the presence and degree of sensitivity after intracutaneous injections before intra-arterial injections. No relationship, however, was found to exist between the hypersensitive state, as evidenced by a positive skin reaction, and the distribution of renal changes.

There was macroscopic enlargement of the involved kidney. Histologically, the lesions varied in severity with proliferation of capillary endothelium and of the epithelium covering the glomerular tufts. An occasional hyaline thrombus and polymorphonuclear cell exudate were observed. There were also periglomerular cell infiltrations, capsular thickening and crescents. Occasional subcapsular deposits of fibrin were found. The tubular epithelium showed degenerative changes, while the lumens contained fibrin and red cell shadows.

Long and Finner produced glomerular lesions in tuberculous swine by injecting tuberculin directly into the renal artery. They claimed

the production of acute exudative glomerulonephritis or occasionally acute interstitial nephritis, followed by "endothelial and epithelial" organization and occasional crescent formation. In animals in which the kidneys were examined one year after injection only small scars remained. Injections of tuberculin into controls had no effect. The authors believed that the response which they observed was allergic.

In the same year McGregor reported exudative and proliferative changes in many glomerular tufts and beginning tubular atrophy in rabbits which had received two injections of B C G vaccine into the renal artery at an interval of fifteen minutes.

The effect of injecting tuberculin into the renal artery was reinvestigated by Long, Huggins and Vorwald. Smaller doses of tuberculin were administered, and the effects were studied in swine, monkeys and goats. The monkeys received human tubercle bacilli intraperitoneally and then coagulated tuberculoprotein intrarenally. The renal lesions were slight. Occasional vascular thrombosis with subsequent necrosis was noted. In goats, the injection of bovine tubercle bacilli caused miliary pulmonary tuberculosis. One animal presented acute interstitial nephritis after the arterial injection. Three goats which received an intrarenal injection of human tubercle bacilli showed only minimal lesions. One animal showed slight tubular degenerative alterations and hyaline casts. In another a periglomerular lymphocytic infiltration was determined at biopsy. Later the kidneys appeared normal. Frequent arterial thromboses, which probably were results of the method of injection, were found. In swine, transient interstitial changes were found, similar to those previously reported, and fatty change of the tubular epithelium. Slight increase in the cellularity of the glomerular tufts was observed occasionally in these animals.

The clinical observation by Blackman, Brown and Rake of glomerulonephritis in from 40 to 50 per cent of patients succumbing to pneumococcic infections led these workers to the use of pneumococci in an experimental attempt to reproduce the disease. Rabbits received from one to nine intravenous injections of sterile pneumococcic autolysate prepared from pneumococci of type I. Of the 44 rabbits given injections, 41 (93.1 per cent) showed some renal change of a focal character. The majority of the kidneys were reported grossly enlarged and pale; a few contained petechial hemorrhages. The earliest histologic changes were hemorrhage within the subcapsular spaces and tubular lumens with colloid droplet formation in the tubular epithelium. The glomerular capillaries contained fibrinous or hyaline thrombi. Later there were capsular adhesions, droplet degeneration of epithelial cells of tufts and necrosis of tubular epithelium with hyaline, fibrinous and red blood cell casts. The walls of a few smaller arterioles were hyalinized.

Later calcification of the tubules appeared with some epithelial regeneration. Intradermal inoculations of an autolysate of pneumococci of type I produced similar abnormalities.

Blackman with single doses of pneumococcic autolysate produced necrosis, calcification and regeneration of the tubular epithelium of rabbits. Repeated doses of toxin equal to or somewhat smaller than the single dose produced, in addition to the changes mentioned, glomerular hemorrhages, fibrinous exudate between the capillary loops, and capillary thrombi. The author concluded, therefore, that nephrosis and glomerulonephritis are essentially the same disease. "The quantity of toxin given, and the degree of immunity which develops during the progress of the disease are important factors in determining the character of the histological lesions in the kidney. . ."

Semsroth reported enlargement of glomerular tufts, capillary dilatation and anemia as the early changes, and ultimately, endothelial swelling and proliferation in rabbits from four to twenty-four hours after the injection of virulent pneumococci of type I. The lesion was believed to be the result of a dilator effect on capillaries. Subsequently Semsroth and Koch reported similar findings. They made intracutaneous injections in 45 rabbits and an intravenous injection in 1 rabbit. In 9 of their animals (20.5 per cent) from four to forty-eight hours after injection there was a diffuse glomerular lesion consisting of endothelial proliferation and enlargement with sparse vacuolation, occasional red blood cells in the subcapsular spaces, general ischemia and frequent hypertrophy of the capsular epithelium. In 6 other rabbits these lesions were described as focal. Fahr, who examined these sections, believed that the lesions closely resembled human glomerulonephritis.

Glomerulonephritis in a male rhesus monkey which had received repeated injections of cultures of Str. viridans over a period of four years was reported by Bell and Clawson. Hematuria was noted frequently during the course of the experiment and was usually found to be more pronounced immediately after an injection. Necropsy showed a small heart and slightly enlarged kidneys. Microscopically there were marked endothelial hypertrophy and hyperplasia with occasional occlusion of the capillary lumens of the tufts, ischemia and reduplication of the hyalinized basement membrane. The lesions were reported to be diffuse.

Helmholz studied the effect of repeated injections of bacteria on the kidneys of rabbits. One group of 24 animals received from one to nine injections (usually intravenous, occasionally subcutaneous and intra-aortic) of hemolytic streptococci isolated from the middle ear of a patient with nephritis. A second group of 8 animals received repeated intravenous and subcutaneous injections of green-producing streptococci

isolated from the urine of a patient also with nephritis. Neither group of rabbits showed nephropathy. A third group of 7 animals was given at monthly intervals three increasing doses of green-producing streptococci obtained from patients with subacute bacterial endocarditis. In order to obtain a chronic abscess 4 of these animals received the primary injection subcutaneously in combination with milk, while subsequent injections and those in the remaining 3 animals were administered intravenously. Capsular proliferation with crescent-like formation, adhesion of tufts to the capsule and hyaline changes were described in 4 of the animals which survived. One animal, which received all injections intravenously, showed especially marked hyaline changes affecting every glomerulus and giving a positive congo red stain for amyloid. The latter, however, could not be elicited in either the liver or the spleen.

Vallery-Radot and his associates in 1933 reported the production of glomerular and tubular lesions, interstitial congestion and rarely interstitial fibrosis in rabbits by daily injections (intravenous, intramuscular and intraperitoneal) of filtrates of cultures of Str. haemolyticus. The precise nature of the glomerular and tubular lesions, however, was not made clear nor were there any photographs. Clinically, the investigators reported azotemia, albuminuria and effusion into serous cavities.

Various routes and combinations of injections of Dick toxin and green-producing streptococci were employed by Rieder and Balzer. The changes reported consisted either of renal infarction or of what can be interpreted as spontaneous interstitial nephritis. Such complicated procedures as subjecting groups of animals to sensitization, exposure to cold, reinfection with streptococci and injection of Dick toxin were productive merely of "embolic" lesions. The combination of the administration of epinephrine and racemic ephedrine (after Wiesel and Hess), sensitization with scarlatina streptococci and subsequently the injection of Dick toxin into the renal artery was similarly unsuccessful. With diphtheria toxin they obtained hyperemia of glomerular tufts and slight degenerative changes of the glomerular endothelium and tubular epithelium.

Dick and Leiter produced amyloid "glomerulonephrosis" by intravenous injection of streptococci. The lesion was either focal or diffuse, depending on the duration of the experiment. The amyloid was limited to the wall of the afferent arteriole at its point of entrance into the tuft, and to one or two loops. Amyloid deposits were also noted within the medullary capillaries. The liver was free and the spleen only occasionally involved.

Patrassi gave rabbits single or repeated intravenous injections of diphtheria toxin and described "focal toxic glomerulonephritis." The histologic observations were classified on the basis of severity and interval after injection but were not correlated with the number of injections:

Group 1 (animals killed within from two to three days after injection). There were necrosis of glomerular loops, hemorrhages either from tufts or from intertubular capillaries, polymorphonuclear cell infiltration (usually perivascular) and enlargement of tufts. The endothelial cells were diminished in number and revealed karyorrhexis of their nuclei. Epithelial cell changes were less pronounced and consisted of a decrease in the size of the nuclei. Hyaline thickening of the capillary walls and infrequent "hyaline" thrombi within the capillaries were noted. The tubular epithelium was swollen, showed hyaline droplet degeneration and desquamation. The interstitial tissue was edematous and occasionally contained polymorphonuclear leukocytes and lymphocytes. In short, this stage was characterized by involvement of all structural units of the kidney.

Group 2 (animals killed within from three to fifteen days). The lesions consisted mainly of focal capillary damage. The basement membrane was irregularly widened, producing narrowing of the lumen. The endothelial cells were increased in number and enlarged early in this stage, while in later stages regressive changes supervened. Dilatation of capillary walls, formation of capillary aneurysms, disappearance of endothelial cells, thrombus formation and fibroblastic proliferation occurred. Bowman's space contained albuminous exudate, erythrocytes and infrequent polymorphonuclears and perivascular aggregates. The tubular epithelium showed sparse degenerative changes; the lumens contained few hyaline casts but many red blood cells.

Group 3 (animals killed within from twenty-two days to three months after injection). Rather widespread damage of glomerular tufts, showing a cellular connective tissue replacement, was found. The walls of the vasa afferentia were thickened and contained an increased number of cells. Infrequent crescents were also noted, plus proliferation of the interstitial connective tissue.

The effect of staphylococci and their filtrates on the kidney has been the subject of study in relatively few investigations. A detailed discussion of the various toxic moieties of staphylococcic filtrates is beyond the scope of this review. It has been generally recognized that staphylococcic filtrates possess at least five toxic fractions, namely,

leukocidin, hemotoxin, dermotoxin (necrotoxin), an "acute killing poison" and finally nephrotoxin.

The nephrotoxic power was first recognized by Neisser and Levaditi. These workers discovered cortical necroses in the kidneys of rabbits which had been given injections of the toxin of Staph. aureus. Histologic study showed foci of necrosis, engorgement of tufts and occasional proliferation of Bowman's capsule. The smaller blood vessels contained fibrinous thrombi or masses of fragmented leukocytes. Neisser and Levaditi attributed the necrotic lesions to the vascular thrombi.

Extensive necrosis of the kidneys of rabbits was produced by Forssman with a single intravenous injection of staphylococcus toxin. Microscopically, widespread hemorrhages into the subcapsular space and epithelial necrosis in the outer cortical zone were described.

Rigdon, Joyner and Ricketts further investigated the effect of single or repeated intravenous injections of a filtrable toxin produced by a hemolytic strain of Staph. aureus. The glomeruli showed occasional hyaline thrombi in capillaries, rare fusion of tufts and desquamated cells and erythrocytes within Bowman's space. Early there was capillary engorgement; later, ischemia. The tubular epithelium presented the most severe lesions—degeneration, desquamation and necrosis; occasional vascular thrombi were also found. These lesions were focal. Rigdon and his associates considered the toxin to be both an epithelial and an endothelial poison.

Rigdon repeated the aforementioned procedure in dogs and rabbits. Among other visceral changes, he described swelling and granularity of the tuft cells and degenerative tubular alterations. In rabbits the renal lesions were most constant and consisted of cortical necrosis and dilatation and static hyperemia of the tuft capillaries. The tubular epithelium often was swollen and contained hyaline droplets. In dogs the lesions were similar except that cortical necrosis was absent.

The effect of the toxin of Staph. aureus on the kidneys of rabbits and cats was studied by von Glahn and Weld. Rabbits were given single intravenous injections and then killed at varying intervals. After two hours, engorgement of the glomerular capillaries and swelling of the tubular epithelium were found. After four hours there were intertubular hemorrhages, dilatation of the glomerular capillaries, fragmentation of the nuclei of the tuft endothelium and occasional necrosis of the walls of the afferent arterioles. Infarct-like lesions were seen in the cortex, while the tubular epithelium was the seat of degeneration and necrosis. Similar but more severe changes were noted in animals killed from eight to twenty-four hours after injection.

Histologic preparations of the kidneys of cats each of which received a single intravenous injection showed focal capillary engorgement, fibrin

within the capillary lumen and infrequent necrosis of portions of glomerular loops. The other viscera did not reveal comparable lesions. Von Glahn and Weld concluded that the in vitro prepared toxin of the hemolytic strain of Staph. aureus had a selective renal effect and primarily injured the blood vessels.

Hämäläinen, who was primarily interested in determining the pathogenesis of nephropathies due to hematogenous staphylococcic infections, administered cultures of staphylococci to rabbits intravenously. In some animals the primary localization of the bacteria was found to occur in the capillaries, particularly in those of the medulla and at the corticomedullary zone. In other animals, however, the bacteria was found in capillaries disseminated throughout all portions of the kidneys. Bacterial thrombi were ultimately formed.

Bacteria of low virulence were found to disappear from the capillaries while the more virulent ones multiplied. With either type, however, the author observed the development of interstitial nephritis, which progressed outward toward the capsule to form subcapsular abscesses and inward to produce pyelitis. The first reaction to the bacteria was hyperemia, which was followed by regressive changes of the tubular epithelium but never by true glomerulonephritis.

Somewhat similar observations were made by Christ, who was also concerned with determining the localization in the kidney of intravenously injected bacteria. Localization was demonstrated within the intertubular capillaries usually at the corticomedullary junction, while passage into the tubule and glomerular involvement were found to occur secondarily. Primary localization of the bacteria took place within the tufts only when the bacterial suspension contained clumps too large to pass through the glomerular capillaries.

Ahlström's extensive studies added support to the accumulating evidence of the importance of allergy in the development of glomerulonephritis. He prefaced his work with a survey of the literature pertaining to this question and a discussion of the relationship of such a state of altered reactivity to certain aspects of the pathology of the human kidney. Dick toxin when injected directly into the renal artery of the normergic animal produced hyperemia and an increase in the number of polymorphonuclear leukocytes in scattered tufts. Larger doses produced occasional loop necrosis, hemorrhage into Bowman's space and degeneration of the tubular epithelium. After repeated doses there was, in addition, a perivascular infiltration which consisted of monocytes, lymphocytes and polymorphonuclear leukocytes. In sensitized animals the perivascular infiltration following single or repeated injections was more marked. The changes reported by Hückel (see earlier paragraphs) were not encountered.

Intravenous injections of horse serum into previously sensitized rabbits produced only sparse round cell infiltration. After intra-arterial injections, however, the perivascular cell infiltrations were more pronounced; in the cortex these were usually situated about the vasa afferentia and associated with hyaline thrombi. Occasionally after repeated intra-arterial injections of serum, there were observed a glomerular cell increase, stasis, intracapillary fibrin and proliferation of leukocytes and endothelial cells, and thickening of the capillary wall. These abnormalities, however, were focally distributed. One animal showed focal arteritis with intimal necrosis, fibrinoid degeneration and leukocytic infiltration of the media. The absence of widespread histologic changes was attributed to the fact that only a small number of glomerular tufts functioned at a given period.

The effects of combinations of horse serum with staphylolysin, diphtheria toxin, cobra venom, uranium nitrate and Dick toxin were then studied in an attempt to localize the hyperergic tissue response (in the sense of Klinge and Knepper, whose work will be considered later). Only the combination of staphylococcus toxin and horse serum induced lesions which were considered allergic in type and which were more pronounced than after the injection of serum alone. Such an enhancement of effect was believed to be the result of injury to the vascular endothelium by the staphylolysin (Shwartzman; Apitz; von Glahn and Weld). Thus, in animals sensitized to horse serum, doses of staphylolysin, too small to produce any change in the kidney by themselves, produced a diffuse type of glomerular lesion if they were followed by repeated injections of horse serum into the renal artery. The changes consisted of intracapillary plasmatic or fibrinous exudate, increase in the number of polymorphonuclear cells, swelling and occasionally proliferation of endothelial cells and ischemia. Larger doses of staphylolysin and horse serum (but smaller than those which produced changes in the control animals) produced extracapillary changes mainly, such as degeneration of the epithelium of the capsules and tubules.

Diphtheria toxin, uranium nitrate, cobra venom or Dick toxin in combination with horse serum, on the other hand, did not excite changes in the kidneys other than those observed following the use of these poisons alone.

On the basis of these findings Ahlström believed that allergy is of extreme importance for the development of glomerulonephritis. He felt, however, that the additional factor of organ susceptibility produced by endothelial damage was necessary in the preparation of the kidney for the action of an allergen. Such a conclusion is similar in a sense to that of Fahr and of Klinge and Knepper.

In collaboration with Isibasi, Masugi attempted to demonstrate further the importance of allergy in bacterial infection by injecting increasing doses of either living bacteria or bacterial vaccine into rabbits intravenously. Single massive doses of living organisms (B. coli, Str. scarlatinae, Str. viridans and Staphylococcus albus) were administered in order to ascertain the effect of bacteria. After single massive doses the investigators encountered foci of bacteria, vascular leukocyte-fibrin thrombi and frequent visceral abscesses.

Massive injections of colon bacilli into animals treated previously with colon bacillus vaccine produced abscesses within the liver and gallbladder with infrequent evidence of organization. Fibrinoid medial degeneration, leukocytic infiltration and edema of blood vessels, claimed to resemble the lesions of periarteritis nodosa, were reported. Pulmonary infarcts associated with thrombotic arterial occlusion were occasionally found. One animal presented endocarditis.

Similar changes were discovered after repeated intravenous injections of increasing amounts of colon bacilli. In 3 of 10 animals which had received fourteen or more doses there were, in addition, however, widespread proliferation of the endothelium of the tuft capillaries with occasional production of syncytium-like projections in the lumens and hyalin-like masses, which occasionally contained leukocytes. Two animals after fourteen and seventeen increasing intravenous doses of colon bacillus vaccine showed slight perivascular round cell accumulations, "plasma-stasis," filling of capillary lumens with plasmatic or albuminous masses, ischemia of the tufts, albuminous casts and blood in the tubules. The other viscera were not especially noteworthy.

Streptococci injected repeatedly in increasing doses induced similar renal lesions but only in animals which had received more than twenty injections.

The histologic lesions following repeated injections of staphylococci were relatively insignificant when compared with those observed in the other groups. Only 3 of 10 animals showed renal lesions and then only after twenty injections. Two revealed only slight and equivocal endothelial swelling. One showed histologic changes which superficially (Masugi) resembled the hydronephrotic contracted kidney in man.

*Comment.*—The renal lesions following single injections of bacteria or bacterial toxins consist of hyperemia, thickening of the walls of capillaries and thrombus formation in capillaries of the glomerular tufts with occasional formation of "aneurysms." Hemorrhage, cellular proliferation of the tuft with concomitant ischemia, infiltration by polymorphonuclear leukocytes and, often, regressive changes have also been described. The tubular epithelium has frequently been found the seat of degenerative lesions such as cloudy swelling, desquamation and even

necrosis. Early interstitial edema, round cell infiltration and hemorrhage have also been observed, while the renal vessels usually revealed but minimal lesions. Except for the results reported by Semsroth and Koch, lesions following single injections have been focal.

Following repeated injections of bacteria or bacterial toxins exaggeration of the individual lesions and more widespread distribution of such lesions have been claimed by Ophüls (1917), Takenomata, Domagk and Neuhaus, Long and Finner, Shwartzman (1928) Bell and Clawson, Lukens, Lukens and Longcope, McLeod and Finney, Vallery-Radot and others (1933), Blackman, Apitz (1935), Masugi and Isibasi, and Ahlström. The lesions following repeated injections of bacteria or bacterial toxins have also been focal despite their widespread distribution and except for the results of Bell and Clawson do not strictly correspond to the human picture.

Virtually negative results, on the other hand, in spite of repeated injections, have been reported by LeCount and Jackson (1914), Faber and Murray (1917), Bloomfield (1919), Leiter, Helmholz (1932) and Rieder and Balzer.

*(To be concluded)*

# Notes and News

**University News, Promotions, Resignations, Appointments, Deaths, etc.**—W. B. Matthews, formerly instructor in pathology at Northwestern University, has been appointed associate professor of pathology in Emory University, Atlanta, Ga., where he succeeds J. C. Norris, who has entered on private practice.

Louisa Hemken, instructor in pathology in the University of Southern California, Los Angeles, died Nov. 20, 1936, at the age of 32 years.

P. A. Duff has been appointed assistant professor of pathology in the school of medicine of the University of Texas, Galveston.

In the Los Angeles County Hospital has been established the Ramón y Cajal Laboratory of Neuropathology for routine as well as investigative work.

A division of experimental medicine has been established in the medical school of the University of Oregon, with E. E. Osgood as the head.

**Walter Reed Medal.**—The first awards of the Walter Reed Medal by the American Society of Tropical Medicine were made on Nov. 19, 1936, at the annual meeting in Baltimore, Md. The medal was conferred on Mrs. Walter Reed by Col. Joseph F. Siler and received by her son, Major General Walter L. Reed. In compliance with the conditions of award to "an individual or an institution in recognition of meritorious achievement in tropical medicine," a second medal was awarded by the society through Richard P. Strong to the Rockefeller Foundation for Medical Research for meritorious achievement in the study and control of yellow fever. It was accepted by Raymond B. Fosdick, president of the foundation.

**The Chandler Medal.**—The Chandler Medal of Columbia University has been awarded to John Howard Northrop, Rockefeller Institute for Medical Research, "for fundamental discoveries concerning bacteria, the constitution of proteins and the chemistry of digestion."

# Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

## Experimental Pathology and Pathologic Physiology

Blood Plasma Protein Regeneration Controlled by Diet. J. B. McNaught, V. C. Scott, F. M. Woods and G. H. Whipple, J. Exper. Med. **63**:277, 1936.

When the proteins of the blood plasma are depleted by bleeding with return of the washed red cells (plasmapheresis) it is possible to bring the dog to a state in which the plasma protein in the circulation is steadily low and the production of plasma protein on a basal diet is uniform. It is then possible to use these dogs in measuring the potency of various dietary factors for the regeneration of plasma protein. Plant and grain proteins are well utilized to form new plasma protein in these test dogs, but soy bean meal probably should be rated at the head of the list. It is utilized with unexpected promptness and favors the production of albumin, in contrast to other plant proteins, which distinctly favor the production of globulin. With long periods of plasmapheresis on basal rations rich in grain proteins there is a lowering of the resistance of these animals to infection. The spleen, brain and stomach with the basal diet show less potency; 10.2, 11.8 and 13.6 Gm., respectively, of tissue protein must be fed to produce 1 Gm. of new plasma protein. Periods of fasting indicate that the dog can contribute only from 4 to 6 Gm. of plasma protein each week—an insignificant contribution, presumably derived from the host's tissue. Infection and intoxication disturb the production of plasma protein in these standardized dogs and may cause a reduction of the output to very low levels in spite of a considerable intake of food. There may be a very sharp drop of the level of the plasma protein during the first day of intoxication. Some of these observations may be of value in a study of clinical conditions associated with hypoproteinemia.

From the Authors' Summary.

Homoiografting of Rat Pituitary Grown in Vitro. W. Haymaker and E. Anderson, J. Path. & Bact. **42**:399, 1936.

Tissue from the pituitary gland may be adapted for homeotransplantation by being cultivated in the plasma and serum of the host prior to grafting.

From the Authors' Summary.

Effect of Nerve Stimulation on the Hyperergic Inflammatory Reaction. J. M. Lasowsky, D. N. Wyropajew and M. N. Jurmann, Virchows Arch. f. path. Anat. **295**:334, 1935.

Rabbits were sensitized by subcutaneous injections of horse serum. From eight to ten days after the appearance of the Arthus phenomenon the sciatic nerve of one extremity was carefully exposed. From five to sixty minutes after this procedure an activating dose of serum was injected into the skin and muscles of both hind extremities, and the exposed nerve was electrically stimulated during a period of from fifteen to twenty minutes. The extremity in which the nerve had not been exposed served as a control. From thirty-five minutes to twenty-four hours later the animals were killed, and the skin and muscle of the control and of the

stimulated extremity were studied histologically. In one series of experiments the nerve was stimulated mechanically. After both electrical and mechanical stimulation of the sciatic nerve a more intense hyperergic inflammatory reaction was observed in the tissues of the stimulated limb. O. T. SCHULTZ.

## Pathologic Anatomy

CUTANEOUS RHEUMATIC NODULES. W. A. ROSENBERG, Arch. Dermat. & Syph. **30**:377, 1934.

A woman aged 46 had erythematous nodules on the fingers and palms. A boy aged 15 with arthritis had nodules on the extremities and chest. Histologic study of the lesions in both patients showed swelling of the endothelial and adventitial cells and perivascular and periglandular infiltrates in the skin. Rosenberg believes that these are the first cutaneous rheumatic nodules to be reported, in contrast to the subcutaneous rheumatic nodules usually found. S. W. BECKER.

CEREBROSPINAL FLUID OF PATIENTS WITH TUMOR OF THE BRAIN. H. H. MERRITT, Arch. Neurol. & Psychiat. **34**:1175, 1935.

Merritt studied the cerebrospinal fluid of 182 patients with tumor of the brain. The fluid was usually clear; occasionally, when there was an associated increase in the protein content, it was xanthochromic. The pressure of the fluid for the most part was increased, but when the tumor was localized in the brain stem or the pituitary body the pressure was usually normal. Choked disk was often associated with normal pressure of the fluid. The number of cells in the fluid was usually normal; in some instances there was pleocytosis, especially when there was a tumor of the pituitary body or of the frontal lobe. The colloidal gold reaction was normal in some cases; in others abnormal curves, typical of dementia paralytica, or meningovascular syphilis, were obtained. The sugar content was normal, and the chloride content was decreased. The ventricular fluid occasionally exhibited changes—xanthochromia, high protein content and an abnormal colloid reaction. Pleocytosis was rare, and the protein content was not as high as in the lumbar fluid. Merritt thinks that a careful comparative study of the character of the fluid (lumbar and ventricular) may help in localizing the tumor, whether it is in the posterior fossa or in the lateral or the third ventricle. It may help in differentiating tumor from abscess of the brain, dural hematoma, cerebral hemorrhage and thrombosis, epidemic encephalitis, syphilis of the central nervous system and other conditions. G. B. HASSIN.

RUPTURED CEREBRAL VARICES. L. L. TUREEN, S. H. GRAY and PAUL WHEELER, Arch. Neurol. & Psychiat. **34**:1274, 1935.

To the twelve cases of cerebral varices recorded in the literature the authors add two: one in a man aged 41, the other in a white girl aged 13. Such varices appear as abnormally enlarged veins and occasionally give rise to symptoms and signs of tumor of the brain or of some other intracranial lesion, for instance, hemorrhages. In both patients there was vast destruction of cerebral tissue from extensive hemorrhages. In the man the arterial tree was of normal structure, but the veins (the temporal, from the cerebral peduncles and the posterior horns of the lateral ventricles) were varicosed. The walls appeared hyalinized, and the elastic fibers, especially in the small veins, were scarce. In the girl hemorrhages filled all the ventricles. There was no evidence of muscle or elastic tissue in the walls of the varicose veins. The etiologic factor in cases of the type described is thought to be a congenital anomaly. The usual localization is in Galen's vein, its tributaries and the ophthalmomeningeal vein. G. B. HASSIN.

SILICOSIS AND TUBERCULOSIS. F. W. SIMSON and A. S. STRACHAN, Pub. S. African Inst. M. Research **6**:367, 1935.

Histologic examination of silicotic lesions shows two types, namely, simple, in which there is no evidence of an infective factor, and infective, in which the presence of an infective factor is shown by focal necrosis or caseation and less frequently by tuberculous follicle formation. The macroscopic characters of simple and infective lesions commonly enable one to distinguish each from the other on inspection with the naked eye. Inoculation into guinea-pigs of preparations of the silicotic lesions which have the characters associated with the infective type of silicosis but which show no positive evidence of tuberculosis have given positive results in the majority of instances. The evidence from examination under polarized light shows that abundant minute birefractive mineral particles are present in all of the presilicotic and silicotic lesions described, and that no such high concentration of mineral particles is observed in the unaffected portions of the lung. Extraction of the mineral residues from normal lungs and from silicotic lungs shows that the amount of such residues is much higher in silicotic than in nonsilicotic lungs and in the former is, in general, in proportion to the degree of silicotic change that is finally reached. In silicosis of the rapidly developing type, in which a fatal issue follows a brief exposure to high concentrations of silicious dust, the residues are conspicuously high. It is submitted that the evidence as a whole demonstrates *(a)* that the retention of silicious dust in the lung is a necessary precursor to the development of silicosis whether in its simple or its infective form, and that the amount of retained dust determines the intensity of the silicotic process which follows, and *(b)* that, although some silicotic lesions are infective from the outset, many others evidence no influence of an infective factor either at their origin or in their further progress. Lesions of the latter type appear to be the outcome of a distinctive reaction of the lung tissue to retained silicious dust.

FROM THE AUTHORS' SUMMARY.

LESIONS OF THE CENTRAL NERVOUS SYSTEM IN TRYPANOSOMIASIS. IVAN BERTRAND, J. BABLET and A. SICÉ, Ann. Inst. Pasteur **54**:91, 1935.

A thorough histologic study was made of the lesions of the central nervous system in two untreated patients who died of African "sleeping sickness." Diffuse meningo-encephalitis with extremely marked infiltration was noted. To the neuroglia and microglia were joined numerous plasmocytes and histiocytes of adventitial or meningeal origin. The morulated cells of Mott were identical with the cells of Russell with fuchsinophilic bodies, which originated at the expense of plasmocytes. Neuroganglionic lesions of the cerebral cortex gave rise particularly to an acute tumefaction. The picture of liquefaction, indicating severe and irreversible degeneration, was absent, contrary to observations in dementia paralytica. Other histologic changes are described and illustrated.

M. L. MARSHALL.

VIRULENCE OF THE HERPES VIRUS. C. LEVADITI, G. HORNUS and P. HABER, Ann. Inst. Pasteur **54**:389, 1935.

The rabbit is susceptible to herpes virus instilled in the nasal fossae. Alterations in virulence are determined at the level of the mucus of the nose (chancre inoculation), and the virus is eliminated by the mucus. To reach the central nervous system and to provoke herpetic encephalopathy there the virus follows the nerves connecting with the nasopharyngeal mucus, especially the olfactory, the trifacial and the cervical sympathetic (afferent neuron?). The tracheopulmonary apparatus does not seem to enter into the dispersion of virus administered by nasal instillation. It is possible to infect the rabbit by mouth and by stomach. On the

other hand, it appears difficult, if not impossible, to initiate the herpetic infection in the neuraxon by introducing the virus into a bend of the small intestine.

FROM THE AUTHORS' CONCLUSIONS.

RELATIONS BETWEEN INFLAMMATORY PROCESSES OF THE LUNG AND REACTIONS OF THE RESPECTIVE LYMPH GLANDS. G. MOTTURA, Arch. ital. di anat. e istol. pat. **6**:443, 1935.

The material selected for study was obtained at autopsy on adults with acute pulmonary inflammation, especially lobar pneumonia. Sections from the involved and free areas of the lungs were fixed in alcohol and examined histologically. The thorax and neck were completely eviscerated, and particular attention was paid to the removal of the posterior mediastinal lymph glands. No pulmonary lymph glands were ever found in a condition of acute reaction if the corresponding lung was free from infection. Lymphoglandular reaction in the lung was constantly an orthograde propagation. Involvement of the regional lymphoglandular apparatus was secondary but constant in pulmonitis. There are on the average four or five lymph glands about the bifurcation of the trachea, and they are twice as numerous on the right side of the tracheal angle as on the left. The lymph glands of the right superior air passages were always in a reactive state whatever was the localization of the pulmonary process. No strict correspondence was observed between single segments of the lungs and single elements of the lymphatic chains taking origin from the lungs; the line of defluxion is extended with other lines which are anatomically connected with it, i. e., parietal, extrathoracic, abdominal, visceral and cervical. Correspondence between pulmonary territory and parahilar lymph glands was absolute only as regards the side, not as regards the affected lobe.

FREDERICK STENN.

THE DETERMINATION OF THE DURATION OF PREGNANCY BY THE ERYTHROCYTE COUNT IN THE CAPILLARIES OF THE CHORIONIC VILLI. L. OHRINGER, Centralbl. f. allg. Path. u. path. Anat. **63**:373, 1935.

From a study of portions of placenta and of blood from the fetal heart the author concludes that the replacement of erythroblasts by erythrocytes in the capillaries of the chorionic villi occurs at a time constant enough to serve as a basis for a histologic method to determine the duration of a pregnancy from portions of placenta. The placentas studied indicated that when all the red blood cells in the capillaries of the chorionic villi are nucleated the pregnancy is not older than two months. When the erythroblasts comprise more than 1 per cent but the erythrocytes predominate the pregnancy is between two and three months. If only erythrocytes are in these capillaries the pregnancy is more than three months. The blood from fetal hearts over 3 months old never contained erythroblasts and served as a check on the examinations of placentas.

The following explanation for the cell change in the villi is offered: 1. In early embryonic life erythropoiesis is general in the body. 2. At a later period the liver takes on this function. 3. In the third month the bone marrow anlage appears and with development assumes the blood-forming duties. [See Ryerson, C. S., and Sanes, S.: The Age of Pregnancy: Histologic Diagnosis from Percentage of Erythroblasts in Chorionic Capillaries, ARCH. PATH. **17**:648, 1934.]

GEORGE RUKSTINAT.

SO-CALLED PRIMARY SCLEROSIS OF THE PULMONARY VESSELS. J. HÖRA, Frankfurt. Ztschr. f. Path. **47**:100, 1935.

An instance is reported. The histologic changes in the smaller arteries were not characteristic. They were interpreted as being the result of severe primary proliferation of the intima causing marked fibrosis with narrowing of the lumen. Intimal proliferation was also seen in the small veins. In addition, small thrombi, some of which were organized, were found in some of the veins. Höra assumes

that the agent responsible for the vessel changes first affects the precapillary and later the postcapillary vessels. This may explain why older changes and connective tissue proliferations were present in the smaller arteries while the postcapillary veins revealed simply intimal proliferations and thrombi. OTTO SAPHIR.

RIDGES AND CELL BUDS OF THE ARTERIES OF THE THYROID. E. KUX, Virchows Arch. f. path. Anat. **294**:358, 1935.

The projections into the lumens of the arteries of the thyroid described by Horne in 1892 and by Schmidt in 1894 appear to be attracting renewed interest. An article by Gilpin on this subject (*Virchows Arch. f. path. Anat.* **293**:257, 1934) was recently abstracted. Schmidt held that the structures under consideration were physiologic adaptations to alterations in thyroid activity. Gilpin believed that they were artefacts. Kux investigated the problem by means of wax plate reconstructions of the thyroids of cats, dogs and human beings. He describes longitudinal muscular ridges of larger arteries and sphincter-like circular protrusions of muscle at the points of origin of smaller branches from the larger arteries. They were most marked in thyroids subjected to stimulation of the sympathetic nerve before removal. He holds that they are physiologic mechanisms for the control and regulation of the arterial circulation of the thyroid. O. T. SCHULTZ.

ARGENTOPHIL DEPOSITS IN THE BRAIN IN CANCER. K. NEUBÜRGER and A. RÖSCH, Virchows Arch. f. path. Anat. **294**:537, 1935.

Argentophil deposits have been observed in the brain associated with senile dementia and in atrophic senile brains without dementia. The chance finding of such deposits in the brain of a woman dead of cancer at the age of 57 years led to systematic search for such deposits in sixty brains from persons who died of cancer between the ages of 40 and 60 years, this period of life being below that at which argentophil deposits have been found. Such deposits were found in nineteen of the brains examined. This finding is interpreted as evidence that cancer is a generalized disease, of which the local neoplasm is only one manifestation.

O. T. SCHULTZ.

EARLY CHANGES IN EXPERIMENTAL SILICOSIS OF THE LUNGS. E. BEINTKER, Virchows Arch. f. path. Anat. **294**:546, 1935.

Although there is a voluminous literature on silicosis, little attention has been paid, according to Beintker, to the early changes in this process. For his study Beintker had the rather clever idea of using the silicious diatomaceous earth, kieselguhr. This contains silicon-encrusted fossil diatoms, which make possible a visualization of the material when inhaled into the lungs. Ten rabbits were subjected to dust-laden atmosphere for a period of five minutes daily for one week. Each successive week the time was increased by five minutes until the animals were subjected to the dust for one hour daily. Five of the animals died within the first fourteen days, three lived, respectively, fifteen, eighteen and twenty-four months, and two died in the intervening period. In the lungs the inhaled material is quickly taken up by phagocytic protective cells that Beintker thinks are derived from the alveolar epithelium. He ascribes phagocytic activity also to cells derived from the bronchial epithelium. Within the lungs the material is transported, both in cells and in the free state, by the lymphatics and mechanically by the movements of the lungs. In the interstitial tissue it leads to the formation of foreign body giant cells. The material sets up a proliferative reaction in the lymphoid tissues which goes on to fibrosis. Involvement of blood vessels leads to the formation of nodules similar to those seen in human silicosis. The nodules are the result of the action of silicic acid. He states that his findings apply only to the rabbit's lung, since human silicosis due to diatomaceous earth has never been observed.

O. T. SCHULTZ.

## Microbiology and Parasitology

SUSCEPTIBILITY OF THE GUINEA PIG FETUS TO VACCINIA. J. STRITAR and N. P. HUDSON, Am. J. Path. **12**:165, 1936.

The virus of vaccinia was successfully propagated in the fetal guinea-pig. The effect of the virus was to induce typical lesions in various organs and tissues. The same strain of virus caused only the slightest reaction in the animal after birth. These results indicate a markedly greater susceptibility of fetal tissues for an infectious agent. The cultivation by other workers of certain viruses in embryonic tissues when adults of the same species were not reactive points to the same phenomenon. The mechanism of this comparative effect is not clear, although the general immaturity and rapidity of cell growth in the fetus are suggested as possible factors. Lesions were found irregularly distributed in the principal organs, including the skin, and were most common in the lungs and kidneys. Of all the fetal tissues, the kidney yielded the virus most constantly and in the highest titer, usually 1 : 10,000. The virus was passed through a series of fetuses and was not appreciably modified in its cutaneous activity in the rabbit or in its failure to induce effects in the guinea-pig after birth. FROM THE AUTHORS' SUMMARY.

SUSCEPTIBILITY OF THE GUINEA PIG FETUS TO THE SUBMAXILLARY GLAND VIRUS OF GUINEA PIGS. F. S. MARKHAM and N. P. HUDSON, Am. J. Path. **12**: 175, 1936.

Infection of the guinea-pig fetus with submaxillary gland virus is described. Typical inclusion bodies were found and were taken as an indication of the presence of the virus. On this basis the virus was apparently generalized throughout the fetus. Lesions appeared in most of the organs, especially the brain, liver and placenta. When death occurred, it seemed to be due to interference with the circulation by lesions in the placenta and liver. The fetus is better suited in many respects for experimental work with the submaxillary gland virus than the newborn or young guinea-pig, since interference from spontaneous infections is avoided, smaller amounts of virus can be detected and the yield of virus is greater. The susceptibility of the fetus is not altered by the immune state of the mother.

FROM THE AUTHORS' SUMMARY.

THE COLONY MORPHOLOGY OF TUBERCLE BACILLI. K. C. SMITHBURN, J. Exper. Med. **63**:95, 1936.

The colonial topography of tubercle bacilli is significantly affected by altering the $p_H$ of the culture medium. Under the conditions of these experiments avian tubercle bacilli produce two colonial variants, rough and smooth. The former are most numerous on the most acid medium ($p_H$ 6); the smooth colonies are obtained over a broad range of $p_H$. Three colonial variants of bovine and human tubercle bacilli are described. These mammalian types produce greater numbers of rough colonies at $p_H$ 6. The bovine strains produce the greatest numbers of smooth colonies in the $p_H$ range of 6.4 to 6.8; they produce intermediate colonies on an alkaline medium. The human strains produce the greatest numbers of smooth colonies at $p_H$ 6.4 and large numbers of intermediate colonies at $p_H$ 6.8 and and $p_H$ 7.2. Included among the avian and bovine strains studied are some of widely varying pathogenic properties. Virulent and attenuated strains of a given type produce similar colonial variants under similar environmental conditions.

FROM THE AUTHOR'S SUMMARY.

A CHANGE IN RABBIT FIBROMA VIRUS SUGGESTING MUTATION. C. H. ANDREWES and R. E. SHOPE, J. Exper. Med. **63**:179, 1936.

A strain of virus of the rabbit fibroma (changed virus) producing partly fibromatous, partly inflammatory lesions is believed to represent a mixture of the original virus with a strain (inflammatory virus) causing only necrotic and

inflammatory lesions. The inflammatory virus does not represent a contamination from without but probably arose as a mutant from the original strain. The occurrence of mutation among viruses and the propriety of using the word in this field are briefly discussed. Consideration is also given to the nature of the change in the virus which leads to a tissue reaction so widely different from that produced by the original strain.

FROM THE AUTHORS' SUMMARY.

PATHOGENESIS OF PNEUMOCOCCUS INFECTIONS IN MICE. G. RAKE, J. Exper. Med. **63**:191, 1936.

Unprepared mice given intranasal inoculations of certain strains of pneumococci will present pneumonia. The proportion of inoculated mice which will show pneumonia at autopsy is dependent on the strain and type of pneumococci and the breed of mice used. It has been shown that, with the technic employed, the pneumococci reach the lower respiratory tract and alveoli almost immediately; moreover, that an invasion of the blood stream occurs very rapidly and can be demonstrated in a third of the mice during the first ten minutes. There is some evidence that invasion of the tissues and the blood stream may occur both through the upper respiratory tract (probably the nasal mucosa) and through the alveolar walls. It is uncertain which route of invasion, if either one, is the more important. It has been possible to produce pneumonia by direct intravenous injection of pneumococci. It may be that pneumonia is favored by a reaction at the point of invasion through the alveolar walls in the intranasally inoculated mice, but the results of the intravenous injections make it clear that such a local lesion is unnecessary for the production of pneumonia in mice.

FROM THE AUTHOR'S SUMMARY.

FAILURE TO INFECT MONKEYS WITH POLIOMYELITIS VIRUS THROUGH ISOLATED INTESTINAL LOOPS. E. H. LENNETTE and N. P. HUDSON, J. Infect. Dis. **58**: 10, 1936.

Suspensions of cords of monkeys with poliomyelitis were instilled repeatedly into loops of isolated bowel in four monkeys (Macacus rhesus), without producing infection. Attempts to induce poliomyelitis by administering whole cord were likewise unsuccessful despite the comparatively huge doses employed. Subsequent efforts were preceded by a preliminary washing out of the loops with phosphate buffer solution, $p_H$ 5, in an endeavor to increase the permeability of the intestinal mucosa. This method, found to be so useful in increasing the incidence of infection by the nasal route, was ineffective when applied to the bowel. Thus, although virus in one form or another was administered intensively over a period of three months no poliomyelitis occurred at any stage of this prolonged experiment.

Neutralizing antibodies were not demonstrated in the serum forty-four days after the last instillation of virus. Saline extracts of the isolated intestinal loops and of the regional lymph nodes draining them failed to inactivate the virus. The virus was not demonstrated in the two extracts tested.

We were unable to find that the virus invades monkeys of this type by the intestinal route when large amounts were applied to the normal mucosa over long periods of time in the absence of the usual intestinal contents.

FROM THE AUTHORS' SUMMARY.

CONTAMINATION OF A BACTERIAL CULTURE BY AN ORGANISM RESEMBLING HARTMANELLA CASTELLANII. L. E. SHINN and P. B. HADLEY, J. Infect. Dis. **58**:23, 1936.

An ameba resembling Hartmanella Castellanii has been found as a spontaneous contaminant in a stock culture of the Friedländer bacillus. Some minor differences in morphology between the cysts of this strain and those of Castellani's strain were observed. The phenomenon of secondary colony formation, resulting

from the transfer of viable bacteria across the agar surface by the amebas, is described. Observations on the response of the amebas to a limited number of bacterial species gave results similar to those reported for H. Castellani. Only superficial resemblance was found between the "lysis" of bacterial colonies produced by amebas and the lysis effected by the bacteriophage.

From the Authors' Summary.

Diffusion Factor in Culture Filtrates. D. McClean, J. Path. & Bact. **42**: 477, 1936.

Filtrates from cultures of Clostridium Welchii contain a factor which causes marked immediate increase in the permeability of the tissues; this factor is active in high dilutions. The diffusing activity does not appear to be related particularly to any one of the various toxins produced by different types of this clostridium. Two other members of the gas gangrene group, Clostridium Chauvei and Clostridium oedematis-maligni (vibrion septique), elaborate varying amounts of a similar factor, while some strains of Clostridium Novyi (oedematiens) produce traces. No increase in diffusion was caused by two samples of Clostridium histolyticum toxin, and no diffusing activity was detected in filtrates from cultures of Clostridium tetani. Filtrates from virulent cultures of type I pneumococcus contain considerable amounts of the diffusing factor, which is not present in cultures of avirulent strains obtained from the virulent cultures by incubation in immune serum. Solutions of the specific polysaccharide of type I pneumococcus show no diffusing activity. Filtrates from cultures of Clostridium diphtheriae of the gravis, mitis and so-called intermediate types contain small and variable amounts of the diffusing factor. No definite evidence was obtained that a correlation exists between the invasiveness of the strain and the amount of the factor that is elaborated. The activity of the diffusing factor is not destroyed by exposure to a 0.4 per cent solution of formaldehyde at room temperature. Exposure at 37 C. causes a fairly rapid destruction of diffusing power.

From the Author's Summary.

Propagation of the Virus of Epidemic Influenza on the Developing Egg. F. M. Burnet, M. J. Australia **2**:687, 1935.

The virus of epidemic influenza has been propagated for fourteen generations on the chorio-allantoic membrane of the developing egg. Characteristic lesions are produced, the macroscopic and microscopic features of which are described. The method may be useful in preparing antigens for immunization against influenza.

From the Author's Summary.

Specific Infectiousness of Syphilitic Ganglions. A. Bessemans, J. Van Hée and J. Van Haelst, Ann. Inst. Pasteur **54**:282, 1935.

Experiments on rabbits, guinea-pigs and mice did not enable the authors to show any infectiousness of inguinal nodes from eight patients with dementia paralytica. Various cutaneous inoculations in attempts to activate the nodes resulted in failure. Superinfection by cutaneous scarification, regardless of the strain of spirochetes, induced no specific reaction. It was, moreover, impossible to repeat the work of Prigge and Rutkowski, according to whom the virus of superinfection did infect the site of inoculation and the adjacent nodes.

From the Authors' Conclusions.

Typhus Fever. Marguerite Ronse, Ann. Inst. Pasteur **54**:341, 1935.

Besides rats, typhus infects gray mice, dwarf mice, meadow mice, the garden dormouse and field mice, as well as hedgehogs and pigeons. Since infection by ingestion of ectoparasites of infected animals resulted in an infection less severe

than otherwise, the relatively great activity of such animals carrying unattenuated virus may well be a factor in transmission. Observation of rickettsias was not a sure means of demonstrating existing infection, nor did the Weil-Felix reaction check in some species of animals. Immunity was correlated with the existence of antiviral substances in the serum, which ordinarily appeared when the virus disappeared.

FROM THE AUTHOR'S CONCLUSIONS.

## Immunology

STANDARDIZATION AND CONCENTRATION OF ANTIMENINGOCOCCUS HORSE SERUM (TYPE I). H. W. SCHERP and G. RAKE, J. Exper. Med. **63**:547, 1936.

Type I antimeningococcus horse serum has been standardized by quantitatively determining the type-specific precipitin content. By a method involving dialysis and precipitation through treatment with carbon dioxide the antibody in such serum has been purified tenfold with respect to the nitrogen content.

FROM THE AUTHORS' SUMMARY.

BLOOD GROUPING OF RWALA BEDOUIN. W. M. SHANKLIN, J. Immunol. **29**:427, 1935.

A determination of blood groups among 320 members of a Bedouin tribe, the Rwala, of the Syrian desert, showed a very high incidence of the 0 group. The percentage of the Rwala showing this group ranged from 64 in one camp to 95 in another of the five camps. The camp with the highest percentage of members showing the 0 group had only 5 per cent showing the A group and none showing the B or A B groups. Among the other camps the highest percentage showing group A was 21, and the highest showing group B was 13. The findings suggest some relation to American Indians and no relation to the other Asiatic races whose blood groups have been studied.

I. DAVIDSOHN.

THE ANTIGENIC PROPERTIES OF BACTERIA COMBINED WITH ANTIBODIES. L. OLITZKI, J. Immunol. **29**:453, 1935.

Bacteria maximally saturated with specific antiserum retained most of their ability to stimulate the production of agglutinins in rabbits. Only by injection of some more free antibodies either before or after the injection of the saturated antigen was it possible to prevent the development of antibodies. By lysing bacteria with phage and then adding a sufficient amount of antibody it was possible to inactivate the antigen completely. The inactivation of the antigen by these procedures was specific, and it permitted one to produce highly specific antiserums.

I. DAVIDSOHN.

THE TOXIGENIC PROPERTIES OF HEMOLYTIC STREPTOCOCCI FROM HUMAN INFECTIONS. A. WADSWORTH and J. M. COFFEY, J. Immunol. **29**:505, 1935.

In all, 471 strains of hemolytic streptococci isolated in various human infections were studied (*a*) as to virulence for mice and (*b*) as to production of toxins for the skin of the rabbit. The neutralization of their toxic filtrates by monovalent antistreptococcus goat serum was tested by intracutaneous injections into goats. The strains isolated in cases of severe suppurative infections (mastoiditis, empyema) possessed higher virulence, but with this exception no relation was noted between the virulence of the strain and the type or severity of the infection in which it was isolated. A slightly higher percentage of toxigenic strains was found among cultures in cases of severe infections and a lower toxigenicity among cultures from the nose, throat and sputum. A marked variation of neutralizing properties was found among various monovalent antistreptococcus serums. The widest range was noted for a goat serum produced by the so-called Dochez N. Y. 5 strain. A few strains were encountered the toxins of which were neutralized by a mixture of three different antiserums but not by any of the three alone.

I. DAVIDSOHN.

THE CAPACITY OF BOILED ERYTHROCYTES TO REMOVE AGGLUTININS. W. C. BOYD and E. H. TAYIAN, J. Immunol. **29**:511, 1935.

While the blood group properties A and B are heat-resistant, the specificity of the factors M and N of human erythrocytes is lost after boiling.

I. DAVIDSOHN.

THE ANTISTREPTOLYSIN TITER IN RELATION TO LATITUDE. A. F. COBURN and R. H. PAULI, J. Immunol. **29**:515, 1935.

The antistreptolysin test was used to determine the presence of recent infections with the hemolytic streptococcus. The tests were made during April 1934 on 416 healthy persons free from rheumatic fever. In 150 persons in large cities below latitude 35 degrees the average titer of antistreptolysin was 71 units, while in 231 persons in localities north of 40 degrees the average titer was 100 units. The results are in agreement with the reported rare incidence of throat infections due to hemolytic streptococci in southern latitudes.

I. DAVIDSOHN.

ACTION OF HUMAN AND ANIMAL BLOOD ON THE MENINGOCOCCUS. N. SILVERTHORNE and D. T. FRASER, J. Immunol. **29**:523, 1935.

The killing action of human blood on meningococci was highly specific and contained in the plasma. By inoculating guinea-pigs with strains of meningococci that were isolated from cerebrospinal fluid immune serums were produced which were strictly specific for the homologous strain. Heating destroyed the bactericidal property of the immune plasma; the plasma could be reactivated by the addition of fresh guinea-pig serum without bactericidal properties.

I. DAVIDSOHN.

INACTIVATION OF THE H ANTIGEN BY DILUTE MINERAL ACID. J. T. DUNCAN, Brit. J. Exper. Path. **16**:405, 1935.

The agglutinability and antibody-absorbing properties of the H antigens of flagellated bacteria are readily destroyed by exposing the organisms to a suitable weak concentration of mineral acid; the appropriate acid concentration for a particular bacterial suspension can be determined by titrating a constant volume of the suspension against a series of falling concentrations of the acid and, after a period, neutralizing the mixtures with sodium hydrate solution and testing them with an H-agglutinating serum to find the limit of acid inactivation. Inactivation is effected very rapidly at 50 C. and less rapidly at 18 C.; it may be advisable to use the lower temperature, although the weak concentrations of acid used caused no apparent damage to the O antigens in a short time at 50 C. No attempt has been made to compare this technic with other methods used for inactivating the H antigens, but it can be recommended for its rapidity and simplicity; it does not involve washing or subjecting the suspension to centrifugation, and it seems to cause little or no damage to the O antigens.

FROM THE AUTHOR'S SUMMARY.

THE VI ANTIGEN OF BACILLUS TYPHOSUS AND ITS CORRESPONDING ANTIBODY. A. FELIX and S. S. BHATNAGAR, Brit. J. Exper. Path. **16**:422, 1935.

The Vi antibody (Felix and Pitt: *J. Path & Bact.* **38**:409, 1934; *Lancet* **2**:186, 1934) produced by immunization with suspensions of virulent strains of Bacillus typhosus in the living state exerts a powerful phagocytosis-promoting action on strains containing Vi antigen, while it is without any effect on strains devoid of this antigen. The Vi antibody excels the O antibody in the phagocytosis-promoting function in the same way as it does in the protective action against attack by strains of high virulence. There is a summation effect in the sensitizing activities of Vi and O antibodies, and their respective modes of action seem to be essentially similar, since both depend on the active participation of complement. The Vi antibody elaborated in response to immunization with formaldehydized Vi antigen is

not identical with that resulting from immunization with the natural Vi antigen contained in the living virulent bacilli. The former is much inferior to the latter, in phagocytosis-promoting activity and in protective power, though there is no difference between the two varieties of antibody in regard to their agglutinating properties.

FROM THE AUTHORS' SUMMARY.

INFECTIOUS MONONUCLEOSIS. N. K. B. KIMBELL and C. J. C. BRITTON, New Zealand M. J. **34**:114, 1935.

The authors report a case of infectious mononucleosis of the glandular type with a large number of the so-called abnormal mononuclear cells in the blood and with a strongly positive Paul-Bunnell test for heterophilic antibodies. The age of the patient (27) and the elevated icterus index (20) are of interest.

I. DAVIDSOHN.

DESENSITIZATION OF PASSIVELY SENSITIZED GUINEA-PIGS. P. GORET, Ann. Inst. Pasteur **55**:103, 1935.

It is indicated by the experiments described here that, contrary to the affirmation of Petragnani, it is easy to desensitize guinea-pigs passively sensitized to egg albumin by Besredka's method, who induced desensitization by progressively increasing doses separated by a suitable interval of time; the duration of anti-anaphylactic immunity thus obtained is from fifteen days to three weeks.

FROM THE AUTHOR'S CONCLUSIONS.

AMINO-ACIDS AND STAPHYLOCOCCUS TOXIN. O. GENGOU, Ann. Inst. Pasteur **55**: 129, 1935.

The production of cytolytic, toxic and necrotizing substances by staphylococci was studied in mediums composed of peptone and various amino-acids. The toxic properties appeared to be due to a single substance, the production of which was particularly accelerated by arginine. The ornithine group of arginine appeared to be the more significant. A latency observed in the rate of toxin production in meat infusions was possibly attributable to the combined arginine; otherwise this substance, when available as such, was immediately utilized.

M. S. MARSHALL.

CHOROID MELANIN AND SERUM FLOCCULATION IN MALARIA. E. TRENSZ, Ann. Inst. Pasteur **55**:208, 1935.

A technic is described whereby photometric examination of malarial serum mixed with a special preparation of melanin indicated specific flocculation. It is claimed that the method shows about the same sensitivity as Henry's technic (Congrès pour l'advancement des sciences, Constantine, 1927) but that the use of the purified melanin seems less likely to give false reactions. Exact titration was possible, and the melanin preparation exhibited useful stability.

M. S. MARSHALL.

FIXED ANTIGENS OF THE TUBERCLE BACILLUS. M. A. MACHEBOEUF, G. LÉVY and M. FAURE, Ann. Inst. Pasteur **55**:547, 1935.

Various properties of a nitrogen-free lipoid substance, rich in phosphorus and acting as a hapten, were observed. The substance was isolated from heat-killed organisms. The complement-fixing hapten reacting with tuberculous serum appeared to be a single lipoid substance or to belong to a restricted group of such substances.

M. S. MARSHALL.

ANTIPLAGUE VACCINE. S. M. MINERWIN, P. N. STUPNITZKI and J. S. TINKER, Zentralbl. f. Bakt. (Abt. 1) **133**:170, 1935.

The authors compared the immunizing effect of a plague vaccine prepared in saline solution with that of one prepared in saccharose solution (150 parts of saccharose in 100 parts of distilled water). Both suspensions were heated at 56 C. up to one and one-half hours, after which they were sterile. Sousliks and guinea-pigs were immunized by subcutaneous injections at five day intervals. After a month, all of the animals and normal controls were infected by injection of ten lethal doses of a virulent strain of Pasteurella pestis. The results indicated that the animals immunized with the saccharose vaccine have distinctly the superior protection—a protection practically the same as that conferred by living avirulent cultures. The authors conclude that the saccharose vaccine merits special consideration in the control of plague.

PAUL R. CANNON.

THE ONE DOSE IMMUNIZATION AGAINST DIPHTHERIA WITH PRECIPITATED ANATOXIN. M. ISABOLINSKI, W. JUDENITSCH and I. LEWZOW, Ztschr. f. Immunitätsforsch. u. exper. Therap. **85**:218, 1935.

Guinea-pigs given a single injection of diphtheria anatoxin that was precipitated with 1 per cent alum or with aluminum hydroxide or with iron hydroxide showed within two months high resistance to diphtheria toxin and a rise of the blood antitoxin. In 60 per cent of the animals small indurations of the skin developed at the sites of injection. They disappeared in from five to seven days. Dissolving the alum-precipitated anatoxin with potassium hydroxide yielded a product of still greater antigenic efficiency. The results of all the experiments were checked by inoculating untreated anatoxin. The alum-precipitated anatoxin was used in 245 children. In 96.8 per cent of them the positive reaction to the Schick test became negative within forty-five days. No bad effects were noted.

I. DAVIDSOHN.

IMMUNE HEMAGGLUTININ IN THE RABBIT AND A NEW BLOOD GROUP FACTOR. P. H. ANDRESEN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **85**:227, 1935.

In the course of the preparation of an anti-M serum a hitherto unknown agglutinin was noted that reacted with the erythrocytes of about 94 per cent of 200 persons. The agglutinin, designated by Andresen as anti-X, occurs only in low concentrations and is easily absorbed. The corresponding new blood group factor X is entirely independent of the systems A B O and M N.

I. DAVIDSOHN.

ANAPHYLAXIS IN FROGS. K. MEZEY and E. BERGER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **85**:262, 1935.

Attempts to produce anaphylactic phenomena in fifteen frogs (Rana esculenta) were not successful. General constitutional changes and the behavior of the whole isolated heart and of the heart muscle strip were studied. The extremely low sensitiveness of the frogs to histamine is in accord with their failure to react to reinjections of proteins.

I. DAVIDSOHN.

THE BACTERICIDAL PROPERTIES OF HUMAN SERUM. E. KESTERMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **85**:268, 1935.

The serums of 24 of 27 normal persons showed moderate to marked killing action against colon bacilli but affected staphylococci and streptococci little or not at all. Considerable variations of the action against colon bacilli were observed in the blood serums of 238 persons who were afflicted with different diseases. A marked decrease of this action was noted in the serums of 43 patients with senile arteriosclerosis, myocarditis, pernicious anemia, intestinal

cancer, chronic nephritis and diabetes. However, the decrease was not regular and not constant. More regular was the increase of the bactericidal action in the serums of patients with different acute infectious diseases.

I. DAVIDSOHN.

## Tumors

STUDIES IN CARCINOGENESIS. M. J. SHEAR and E. LORENZ, Am. J. Cancer **26**:322 and 333, 1936.

*Production of Tumors in Mice with Hydrocarbons.*—Tumors have been produced in pure strain mice by subcutaneous injections of crystals of 1, 2, 5, 6-dibenzanthracene, 1, 2-benzpyrene and methylcholanthrene. Cholanthrene similarly administered produced tumors about as rapidly as methylcholanthrene. Methylcholanthrene-choleic acid, an addition compound of the hydrocarbon with desoxycholeic acid, which is soluble in an aqueous medium, produced tumors as rapidly as methylcholanthrene. Tumors were also obtained by the administration of an aqueous solution of the addition compound. Cholesterol pellets made by dissolving the hydrocarbon in molten cholesterol were also employed to produce tumors.

*Detection of Di-Benzanthracene in Mouse Tumors Induced by Hydrocarbons.*—A method is described for the identification and quantitative determination of 1, 2, 5, 6-di-benzanthracene by means of absorption spectrum analysis. Dibenzanthracene may be readily identified to a concentration of approximately 0.01 mg. per cubic centimeter. If known to be present, it can be detected to a concentration of approximately $4 \times 10^{-5}$ mg. per cubic centimeter. Substances present in the lipoid fraction of tumors and showing continuous absorption in the region of the dibenzanthracene absorption spectrum can be largely removed by chemical procedures. Tumors induced by a lard solution of dibenzanthracene were found to contain an appreciable amount of the hydrocarbon. Fifth and sixth generation transplants of these dibenzanthracene-induced tumors failed to show the presence of dibenzanthracene.

FROM THE AUTHORS' SUMMARIES.

THE ENZYME CONTENT OF A PARENCHYMATOUS ADENOCARCINOMA OF THE PANCREAS. K. SUGIURA, G. T. PACK and F. W. STEWART, Am. J. Cancer **26**:351, 1936.

A pancreatic tumor and three normal pancreases from man were studied to determine their lytic action on starch, on casein and peptone and on seven esters. Under comparable conditions the rate of digestion of starch, the degree of protein hydrolysis and the degree of hydrolysis of esters by the extract of the pancreatic tumor were essentially the same as for the extracts of the normal pancreases. The pictures of the relative ester-hydrolyzing actions of the two tissues were very similar. These results suggest that this tumor had a physiologic as well as a morphologic resemblance to the normal pancreas.

FROM THE AUTHORS' SUMMARY.

THE MORPHOLOGY OF THE SARCOMAS PRODUCED BY 1, 2, 5, 6-DI-BENZANTHRACENE. C. D. HAAGENSEN and O. F. KREHBIEL, Am. J. Cancer **26**:368, 1936.

Fifty-three neoplasms were produced in mice, rats and rabbits by subcutaneous injections of 1, 2, 5, 6-dibenzanthracene suspended in paraffin. They included fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma and squamous cell carcinoma as well as a number of sarcomas which could not be classified. It is possible by means of these new cancerigenic hydrocarbons to produce a wide variety of tumors in many different tissues and to study the morphologic and biologic characteristics of the tumors during their continued transplantation.

FROM THE AUTHORS' SUMMARY.

INTRATHORACIC SYMPATHOBLASTOMA. T. T. FROST and S. E. WOLPAW, Am. J. Cancer **26**:483, 1936.

A sympathoblastoma, probably arising from the inferior cervical sympathetic ganglion, produced the characteristic syndrome of tumor of the superior pulmonary sulcus.

BRONCHOGENIC CARCINOMA. R. S. ROSEDALE and D. R. MCKAY, Am. J. Cancer **26**:493, 1936.

Of 466 cases of cancer examined post mortem at the Buffalo City Hospital during the past ten years, 7.5 per cent were instances of bronchogenic carcinoma. Bronchogenic carcinoma occurs most frequently at or near the hilus of the lung, commonly originating in a bronchus of the first order; there is usually a single massive growth at one hilus. The tumor may metastasize widely. Bronchoscopy with removal of tissue is a most valuable diagnostic method. Rosedale and McKay emphasize that bronchogenic carcinoma must be considered in the diagnosis of all obscure diseases of the chest in patients over 30 years of age.

SPONTANEOUS LEUKEMIA AND CHLOROLEUKEMIA IN THE RAT. S. L. WILENS and E. E. SPROUL, Am. J. Path. **12**:249, 1936.

The spontaneous development of myeloid, chloromyeloid and lymphatic leukemia in a strain of inbred albino rats is described. The total incidence of leukemia in this strain was 3.3 per cent. The disease occurred chiefly in animals over 2 years of age at death and never in those under the age of 18 months. It is somewhat more common in males than in females. No dietary influence on the development of the disease was observed. The pathologic changes conform in most respects to those in other species, including man. One incidental finding not described in leukemia of other species is the colloid droplets in the convoluted tubules of the kidneys. The nature of this nephrosis is unexplained. Lipoid-containing phagocytes are almost constantly associated with the extravascular accumulations of myeloid cells. No histologic differences between the pigmented and nonpigmented forms of the disease were recognized.

FROM THE AUTHORS' SUMMARY.

MIXED TUMORS OF THE PALATE. A. B. ABSHIER, Arch. Dermat. & Syph. **32**:622, 1935.

Abshier reports six cases of mixed tumor of the palate of from two to fifteen years' duration. He quotes Eggers as having found mucoid connective tissue in 76 per cent of eighty-seven cases, cartilage in 38 per cent, glandular epithelium in 96 per cent and squamous epithelium in 37 per cent. The lesions vary from one the size of a small pea to a mass filling the entire oral cavity. The surface is covered with normal-appearing mucous membrane, which is either smooth or thrown into corrugations.

S. W. BECKER.

TUMORS OF THE SPERMATIC CORD, EPIDIDYMIS AND TESTICULAR TUNICS. G. J. THOMPSON, Surg., Gynec. & Obst. **62**:712, 1936.

Tumor of any of the structures named is rare. The twenty-six cases of tumor of the spermatic cord reported include twenty-one of lipoma, one of fibroma, one of hemangioma, one of cystadenoma, one of fibrosarcoma and one of myosarcoma. Included in thirteen instances of tumor of the epididymis are one of dermoid cyst, one of cystadenoma, four of angioma and seven of carcinoma. The tunica vaginalis was involved twice, once by fibroma and once by cystadenoma.

FROM THE AUTHOR'S SUMMARY. (WARREN C. HUNTER.)

INTRACUTANEOUS IMMUNIZATION AGAINST MOUSE SARCOMA. A. BESREDKA and L. GROSS, Ann. Inst. Pasteur **55**:491, 1935.

A preliminary injection of an emulsion of normal organs is, in a certain number of cases, capable of protecting the mouse against sarcoma, but the protective power does not exist in the presence of a very virulent strain.

Emulsions of organs, of embryonic tissue, of avirulent, and of virulent sarcoma given in small doses do not protect the mouse against virulent sarcoma, no matter how the latter or the emulsion may be given.

A specific immunity to sarcoma is produced in the mouse on preparation of the skin with a quantity of weak sarcoma sufficient to produce a resorbable intracutaneous tumor.

FROM THE AUTHORS' CONCLUSIONS.

LEUKOSIS AND SARCOMATOSIS OF CHICKENS: UNITY OF VIRUS. J. TROISIER and J. SIFFERLEN, Ann. Inst. Pasteur **55**:501, 1935.

1. Fusocellular fowl sarcoma of the mesentery was inoculated in the muscle of a chicken; two months later the bird died with complete leukemia.

2. Inversely, the inoculation of two strains of leukemic material in the pectoral muscle resulted in tumor, at the point of inoculation (osteochondrosarcoma, fusocellular sarcoma with myxoid zones).

3. Intravenous inoculation of leukemic blood resulted in generalized sarcomatosis.

4. With two strains passages were obtained. With one, at the third passage, a virus which induced two sarcomas recovered its original property of producing leukemia. With the other, the leukemic virus yielded successive passages of sarcoma without actual return of leukosis.

5. The appearance of leukemia in a chicken inoculated with sarcoma, the appearance of sarcoma at the point of inoculation of leukemic material, the identical filtrability of the two viruses and the appearance of leukosis in the course of passages of a strain of sarcoma which was originally leukemic are other arguments in favor of the hypothesis that the viruses are one.

FROM THE AUTHORS' RÉSUMÉ.

CYSTIC LYMPHANGIOMA OF THE ADRENAL GLAND. H. WINTER, Centralbl. f. allg. Path. u. path. Anat. **63**:305, 1935.

A tumor 5.8 by 3.5 by 3.5 cm. was found in the upper pole of the left kidney of a woman 36 years old. She had died of pneumonia, and no clinical symptoms referable to the tumor were noticed. The mass was composed of five separate cysts containing lymphlike fluid and covered by adrenal cortex. Histologically the cyst wall consisted of connective tissue, in some regions hyalinized, in others calcified. Endothelium was seen irregularly lining the cyst cavities, but no new lymph channels were visible. In neighboring regions of the adrenal gland rows of small cysts with characteristics similar to the main mass were noted. This unusual tumor is believed to belong to the type of lymphangioma that is due to the formation of superfluous lymph ducts which fail to make contact with the lymphatic system.

GEORGE RUKSTINAT.

PRODUCTION OF CANCER IN RABBITS WITH TOBACCO TAR. LÜ-FU-HUA, Frankfurt. Ztschr. f. Path. **47**:52, 1935.

Lü-Fu-Hua endeavors to explain the development of isolated tumors instead of a diffuse tumor in regions diffusely irritated with tobacco tar. He postulates the presence of cells which, though showing no abnormal histologic characteristics, nevertheless possess pathologic qualities or are "potential tumor matrix" of the second order. As "potential tumor matrix" of the first order he defines cell complexes which reveal actual pathologic changes. The "potential tumor matrix" of the second order is the basis of all experimental tumor production, as potential

tumor cells are apparently distributed over the entire body. The development of experimentally produced tumors at a distance from the point of irritation seems proof to the author of his hypothesis. He regards the theory of excessive regeneration as of secondary importance. Another important factor in the experimental production of cancer is the general predisposition of the body, which may be induced artificially with intravenous injections of tar or feeding of cholesterol. According to the author, the changes in the metabolism of the pretreated animals are similar to those found by Warburg in cancer cells and by other authors in regenerating tissues and in animals poisoned with arsenic, tar, indole, etc. He believes that by coordination of all these facts a working theory of the experimental production of cancer may be found. OTTO SAPHIR.

PATHOLOGIC CHANGES IN PRIMARY CANCER OF THE LUNG. I. A. KRAFT, Ztschr. f. Krebsforsch. **41**:51, 1934.

This report is based on a postmortem study of 150 cases of primary pulmonary carcinoma observed at the Metschnikoff Hospital in Leningrad during the years from 1925 to 1932. The incidence of pulmonary carcinoma was exceeded only by that of carcinoma of the stomach and esophagus. Males predominated in the ratio of 11.5: 1, with the greatest incidence in the seventh decade of life. There was no noteworthy difference in the primary site; in this series the left lung was involved somewhat more frequently than the right. The macroscopic findings varied greatly, but Kraft believes that the cases can be separated into two main groups: those in which the cancer originates in a larger bronchus (of first or second order) and those in which it originates in one of the smaller branches. Growth may take the forms of intrapulmonary or extrapulmonary spread, the latter at times being associated with limited growth of the primary cancer. Intrapulmonary growth may occur either in the alveoli or in the interstitial tissues; not infrequently the two forms may be associated. Metastases aside from lymphatic extension were frequent, with especially common involvement of the adrenals. Kraft recognizes four types: (1) undifferentiated small cell cancer; (2) polymorphocellular cancer; (3) flat cell cancer and (4) cylindric cell cancer. Intermediate transitions among the first three are not uncommon. He regards all these types as originating in the bronchi, a feature he was always able to establish by careful dissection. The variant cellular characteristics he believes to be simply manifestations of the developmental potencies of the basal cells of the bronchial epithelium. A high incidence of association with pulmonary tuberculosis was observed—46.7 per cent. The cancer did not appear to accelerate the progress of the infection, and because of the frequent association of the former with old tuberculous scars, he believes that the rôle of the infection in the induction of the cancer is that of a chronic irritant. H. E. EGGERS.

LYMPHO-EPITHELIOMA AND RETICULOSARCOMA. E. VON ZALKA, Ztschr. f. Krebsforsch. **41**:139, 1934.

According to von Zalka, the so-called lympho-epithelioma is by no means rare. It may originate both from epithelial reticulum and from lymphoid cells of histiocytic origin. A similar histologic picture is shown by the reticular sarcoma, but this, with impregnation methods of staining, shows a definite reticulum, whereas a reticulum is lacking in the other. The differentiation is of clinical importance, as the lympho-epithelioma is more sensitive to radiation. H. E. EGGERS.

## Technical

A NEW METHOD FOR STAINING FAT. R. KAWAMURA and T. YASAKI, Centralbl. f. allg. Path. u. path. Anat. **64**: 177, 1936.

A 40 per cent sudan III-alcohol colloidal solution is best for staining fat in tissues.

*Stock Solution.*—The stock solution is made as follows:

1. Triturate 4 Gm. of sudan III.
2. Add 450 cc. of 95 per cent alcohol and heat to boiling over a water bath.
3. Filter. Place in the ice chest for from twelve to twenty-four hours.
4. Filter. Dilute to an 80 per cent alcoholic solution with distilled water. The water must be added drop by drop from a buret and the mixture stirred constantly. Let stand at room temperature for from twelve to twenty-four hours.
5. Filter. This is the stock solution and must be clear.

*Staining Solution.*—To 50 cc. of the stock solution add about 2 cc. of distilled water. Shake the mixture vigorously about twenty times. Repeat this procedure until the total volume is 100 cc. The solution remains stable for several days. It must be filtered before use.

*Staining.*—Tissues fixed in a standard solution of formaldehyde and embedded in gelatin are cut 10 microns thick by the frozen section method.

1. Stain by the Böhmer or Hansen hematoxylin method for ten minutes.
2. Differentiate in 1 per cent sodium chloride solution.
3. Wash in water until sections appear blue.
4. Wash in distilled water.
5. Immerse in sudan III-alcohol solution at 29 to 30 C. for about five hours.
6. Wash in distilled water.
7. Mount with glycerin.

Paraffin sections (Ciaccio method) 5 microns thick may be used in lieu of frozen sections. Before staining, the paraffin must be dissolved away, and the sections then passed through alcohol and washed in water. The only difference in the staining method is that the sections are placed in hematoxylin for twenty minutes.

By these methods all lipoid substances in the tissues appear as brilliant yellow-red granules or droplets. Furthermore, it is possible to demonstrate lipoids in tissues when older methods have failed. Chemical determinations, therefore, are approximated more closely by this fat stain than by any other method. The greater staining power of the sudan III-alcohol solution prepared by Kawamura and Yasaki is due to its colloidal disposition.

LOUISA HEMKEN.

COMMENT ON THE KAWAMURA-YASAKI FAT STAINING METHOD AND A MODIFICATION IN PREPARATION OF THE STOCK SOLUTION. R. KAWAMURA and T. YASAKI, Centralbl. f. allg. Path. u. path. Anat. **64**: 181, 1936.

The precipitation which occurs when tissue is fixed in solution of formaldehyde is unavoidable. The deposits can be removed in the following manner:

1. Place sections in 30 per cent alcohol.
2. Immerse sections in 1 per cent potassium hydroxide solution for about thirty to sixty minutes.
3. Wash thoroughly in 30 per cent alcohol, then in distilled water.
4. Place in hematoxylin and continue with the staining as outlined in the original method.

It is imperative to stain sections at 29 to 30 C; with higher temperatures precipitation occurs.

The time of preparation of the stock sudan III-alcohol solution can be shortened twenty-four hours by using 82 per cent alcohol. The solution is filtered and placed in the ice chest for from twelve to twenty-four hours. Refilter. This is the stock solution. The shorter time does not diminish the tinctorial power of the staining solution.

LOUISA HEMKEN.

# Society Transactions

## NEW YORK PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, May 28, 1936*

N. CHANDLER FOOT, *President*

MILTON HELPERN, *Secretary*

HODGKIN'S DISEASE INVOLVING THE STOMACH, WITH FATAL HEMORRHAGE. JULIUS REDISH (by invitation).

A patient exhibiting involvement of the stomach by Hodgkin's granuloma has recently come to necropsy at Bellevue Hospital. The acute termination of the disease in death due to hemorrhage from the gastric lesion is noteworthy.

A 54 year old white man entered the hospital for removal of a painless enlarging mass of the anterior wall of the chest. The patient had recently experienced gaseous eructations but no other gastric symptoms.

A mass 4 by 6 cm. was palpated in the third left intercostal space at the sternal edge. The liver was palpable 4 fingerbreadths below the costal margin and the spleen 3 fingerbreadths below the costal margin.

Hematemesis suddenly occurred two days after admission and continued to the time of death two days later.

At autopsy the stomach was dilated with partially clotted blood. Two ulcers, one 7 and the other 2 cm. in diameter, were present on the lesser curvature. The margins were elevated and poorly defined. The base of each ulcer consisted of firm white tumor-like tissue 1 cm. in thickness and was covered by a layer of necrotic débris. The overlying serosa was intact.

The peripancreatic lymph nodes, the majority of which were discrete, varied from 0.5 to 5 cm. in diameter and were firm, fleshy and light grayish brown. A few periportal and periaortic nodes were similar but smaller. The spleen was enlarged and studded with well circumscribed white nodules about 2 cm. in diameter. A mass grossly resembling the peripancreatic nodes was found in the third left intercostal space, which was adherent to the sternum and costal cartilage but not attached to the overlying skin.

Microscopic sections through the floor of the ulcers, the splenic nodules, the mass in the thoracic wall and the aforementioned lymph nodes revealed typical Hodgkin's granuloma with many mononucleated and multinucleated giant cells as well as lymphocytes, fibroblasts and occasional eosinophils and plasma cells. Some of the sections appeared cellular; others presented a dense hyaline fibrous stroma.

### DISCUSSION

ALFRED PLAUT: The elevated margin of the ulcer described by Dr. Redish especially interested me. The situation of an ulcer on a plateau seems to be a characteristic of several of the rarer types of gastric ulcer. I am showing a lantern slide of an ulcer of the stomach which my associates and I had the opportunity of seeing in a patient with Hodgkin's disease several years ago. The ulcer is annular. When I saw the gross specimen my first guess was that of a syphilitic ulcer, in spite of the great rarity of such an ulcer. Of the two specimens of true syphilitic gastric ulcer which I remember having seen, one looked exactly like the gastric ulcer the picture of which is shown here. In this patient with Hodgkin's disease the only other granulomatous lesion was in a perigastric lymph node. It is not my intention to show that I, too, have seen this rare disease. I want to lay

stress on the plateau-like character of ulcers which do not fall into the group of ordinary ulcers of the stomach. In a certain number of cases this also applies to tuberculous ulcers of the stomach.

Our patient gave the picture of gastric ulcer with hemorrhage.

THE HISTOLOGY OF A HOMOPLASTIC ADRENAL TRANSPLANT THAT SURVIVED FOR EIGHT MONTHS IN A PATIENT WITH ADDISON'S DISEASE. FREDERICK A. HEMSATH.

The clinical features of this case have been presented before a recent meeting of the American Society for the Study of Internal Secretions.

A white unmarried salesman aged 27 was admitted to Christ Hospital, Jersey City, N. J., on Nov. 30, 1935, because of weakness. This was his only admission to this hospital. In childhood he had had measles and chickenpox, and at the age of 11, severe scarlet fever. The present illness, diagnosed as Addison's disease, was of two and one-half years' duration, and on several occasions remissions had followed intravenous administration of saline solution in other hospitals. During a crisis in March 1935, in another hospital, there was transplanted into the left abdominal rectus an adrenal gland from a healthy woman of the same blood group. The gland had been cut into narrow strips. Marked clinical improvement was reported, which persisted for about six months and was followed by recurrence of weakness, vomiting, low blood pressure and accentuation of pigmentation. On December 3, three days after admission to Christ Hospital, the patient showed clinical evidence of pneumonia and died the same day.

This case first came to my attention when I performed the autopsy two hours post mortem. Pigmentation of the skin and of the buccal mucosa was present, and there were signs of status thymicolymphaticus. The adrenal glands showed complete simple atrophy of the cortex. A small area of bronchopneumonia was present. In the left abdominal rectus muscle were four masses of yellow tissue averaging 6 by 4 by 2 mm., and other minute remnants were seen microscopically. Stained preparations showed the yellow tissue to consist of cells resembling spongiocytes of the adrenal cortex, and frozen sections showed them heavily laden with anisotropic material. The tissue was well vascularized, and groups of cells resembling those of the glomerular zone were present. Adrenal medullary tissue was not seen. The cellular infiltration was limited to a few lymphocytes and endothelial phagocytes together with fat-laden giant cells. A modified Bielschowsky stain showed the yellow tissue to possess a reticulum resembling that of the adrenal cortex. A careful study was made of the fibrosis associated with the transplanted tissue. The transplants for the most part were sandwiched between striated muscle and a dense layer of fibrous tissue. While a certain amount of the fibrosis was conceivably the result of operative trauma, the presence of minute groups of spongiocytes surrounded by fibrous tissue and the fibrous strand infiltration between columns of spongiocytes recalled the fibrous destruction of homoplastic transplants as described by Loeb.

DISCUSSION

S. MILTON RABSON: May I know the circumstances under which the transplant was obtained?

FREDERICK A. HEMSATH: The circumstances of obtaining the transplant as they were reported in the staff meeting at Christ Hospital by the surgeon who operated were that the adrenal gland was obtained from a woman who was overweight and had other evidences of what endocrinologists consider as hyperadrenalism. The group which did the work had obtained marked reductions in weight under these circumstances by removing one adrenal gland. The adrenal gland used was from such a person, a woman who aside from the obesity was healthy and of the same blood group as the recipient. The gland was removed surgically; the surgeon who removed the gland left immediately on completing the operation, cut the gland into narrow strips and immediately inserted it into the abdominal rectus muscle of the recipient.

HEMORRHAGIC EXTRAVASATIONS INTO VALVULAR LEAFLETS AND THEIR RELATIONSHIP TO PULMONARY EMBOLISM. EUGENE CLARK and (by invitation) ADOLPH R. BERGER.

This article will be published in full in the ARCHIVES OF PATHOLOGY.

HEREDITARY EARLY DEATH IN LOCALIZED NEURONS WITH RESULTING PARALYSIS IN DOGS. CHARLES R. STOCKARD (by invitation).

This article will be published elsewhere in full.

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## CHICAGO PATHOLOGICAL SOCIETY

CARL W. APFELBACH, *President*

*Regular Monthly Meeting, Oct. 12, 1936*

EDWIN F. HIRSCH, *Secretary*

### PRESIDENTIAL ADDRESS

MODERN CONCEPTS OF CIRRHOSIS OF THE LIVER. C. W. APFELBACH.

The proceedings of the first and second conferences of the International Society of Geographical Pathology in 1931 and 1934 deal in large part with cirrhosis of the liver. The data accumulated from many countries create authoritative standards with which one can compare the previously held concepts of this disease.

Askanazy, Fiessinger, de Josselin de Jong and Rössle formed the committee on definition and classification. A definition acceptable to this committee indicates three essential types of changes: degenerative changes leading to the disappearance of hepatic cells; a chronic inflammatory reaction occurring at the peripheries of the altered lobules; regeneration of an imperfect type. The disease is chronic and universal in the liver.

Askanazy suggested that this definition might be used in a broad sense so as to include fatty cirrhosis, Laënnec's cirrhosis, pigmentary cirrhosis, syphilitic cirrhosis, Wilson's disease, subacute yellow atrophy, splenomegalic cirrhosis, cholangitic cirrhosis and parasitic cirrhosis. The other members of the committee, however, did not agree to such a broad use of the term "cirrhosis." They did not include the disseminated lesions such as cholangitic cirrhosis, subacute yellow atrophy, parasitic cirrhosis and infectious cirrhosis. The term "Laënnec's cirrhosis" was acceptable to the committee and includes about 60 to 70 per cent of all forms of cirrhosis.

Attention was called to many instances of limited inflammatory reactions in the periportal regions that are difficult to classify. Mallory similarly described a large group of such lesions several years ago.

Concerning the etiologic factors of cirrhosis, there is considerable basis for believing that they are in the nature of a constellation of causes rather than single factors. Ethyl alcohol is generally disregarded as an adequate cause of Laënnec's cirrhosis. It may be the carrier of noxious substances. It may reduce the protection ordinarily enjoyed by hepatic cells against many harmful substances. The characteristic change in the liver in the patient addicted to alcohol is the fatty form of cirrhosis.

The rôle of infection in the production of cirrhosis has been reemphasized by McMahon, Mallory and Moon. The high incidence of cirrhosis in Switzerland, where thyroid disease is prevalent, has suggested to some investigators that hyperthyroidism may be one of the predisposing causes of certain forms of Laënnec's cirrhosis.

Tar products have produced typical Laënnec's cirrhosis in experiments on animals.

The demonstration in animals that diets high in carbohydrates limit the speed of development of cirrhosis and that diets high in protein and fat accelerate its development has especial significance so far as therapeutic measures are concerned.

An analogy exists between the change in the concepts of Bright's disease during the last twenty years and the changing attitude toward cirrhosis of the liver. The kidneys are no longer considered as presenting the essential anatomic alteration in glomerulonephritis and nephrosclerosis. These diseases are generalized, involving many organs. The renal changes are only part of the widely spread disease. Similarly in some forms of cirrhosis of the liver, especially those associated with splenomegaly, anemia, icterus and cerebral degenerations, the hepatic lesions are only one manifestation of a generalized disease in the body.

A significant defect in the study of cirrhosis in the past was brought out in the proceedings of the International Society of Geographical Pathology. Studies of marrow, cerebrum, glands of internal secretion and lymph nodes were sparse, and this made it difficult for the collaborators to describe adequately the associated pathologic conditions of cirrhosis of the liver.

THE WELTMANN SERUM TEST. S. A. LEVINSON, R. I. KLEIN and P. ROSENBLUM.

Although the mechanism of the Weltmann reaction is not known, our studies and those of European investigators indicate that the test is a valuable diagnostic procedure. Weltmann's test is not specific for any disease but reflects the pathologic process predominant in the body. Exudative, inflammatory and necrotic processes are reflected in the blood serum as a shift to the left or a shortened band of coagulation, while fibrotic processes and hepatic parenchymal damage cause a shift to the right or a lengthening of the band of coagulation.

Our findings indicate that the test is of value in distinguishing septic from nonseptic febrile conditions, acute suppurative and gangrenous appendicitis from catarrhal appendicitis, and active rheumatic carditis from endocarditis lenta. In chronic conditions like tuberculosis the Weltmann test is an additional index of the activity of the disease, with respect to the exudative and productive phases. It must be borne in mind, however, that when exudation and fibrosis occur together or when a state of acute inflammation is accompanied by considerable damage to the liver the Weltmann reaction may be inconclusive because of the interaction of the divergent processes.

There is no general parallelism between the Weltmann and the sedimentation test, but a shortened band of coagulation is generally accompanied by rapid sedimentation.

A complete report will be published elsewhere.

RENAL TUBERCULOSIS. FREDERICK LIEBERTHAL.

The tuberculous process in the urinary tract usually begins in the kidney. The original lesion is a small tubercle, which is situated most commonly in the cortex but occasionally in the medulla. Perforation of a renal tubule or of Bowman's capsule may lead to dissemination of tubercle bacilli into the lumen of the tubule. The organisms are then carried down to the corresponding renal papilla, where a caseous ulcer develops. The caseous center of the latter, which contains the organisms in large numbers, serves as a focus from which bacilli are disseminated into the renal pelvis, where they mingle with the urine. An infection of the mucous membranes of the calices, of the renal pelvis, of the ureter and of the urinary bladder follows. The lesions in the ureter soon lead to obstruction and stagnation of tuberculous urine in the renal pelvis. This gives the organisms an opportunity to attack the remaining renal papillae. Caseous erosion of the latter progresses until the small arteries supplying the renal substance are per-

forated and tubercle bacilli are disseminated into their lumens. The organisms are then carried by the arterial blood stream and scattered through the renal substance, where numerous tubercles develop.

Involvement of the wall of a renal artery by a spreading tuberculous lesion may lead to narrowing of the lumen of the vessel so that the flow of blood is retarded, and the resulting ischemia causes sclerosis of the area of tissue supplied by the vessel. Thrombosis may also develop in the lumen of the involved vessel, and this condition leads to the development of an anemic infarct, which may later undergo caseation.

Perforation of venous branches by tuberculous lesions in the kidney leads to dissemination of tubercle bacilli into the major venous circulation and hence usually to metastatic lesions in the lungs.

Clinically renal tuberculosis is usually unilateral, and pathologically it is usually bilateral. Renal tuberculous lesions which are not in open communication with the renal pelvis cannot be diagnosed clinically. Early in the course of the disease cortical lesions appear in the second kidney as the result of infection of the blood stream. The second kidney also becomes extensively involved as the result of infection ascending the urinary passages.

The renal lesion is never primary but is always secondary to some other focus, which is usually in the lungs.

In renal tuberculosis the causes of death are (1) uremia (due to destruction of the secreting parenchyma of both kidneys), (2) generalized amyloidosis and cachexia, (3) pulmonary tuberculosis (due to reinfection of the lungs) and (4) miliary tuberculosis.

GANGLIOGLIONEUROMA OF THE SPINAL CORD. BEN W. LICHTENSTEIN and HOWARD ZEITLIN.

Ganglioglioneuroma of the spinal cord is rare. It is believed that the growth arises from embryonic cell rests of multipotential neurocytes. By the differentiation of these cells, ganglion and glial cells as well as large numbers of nerve fibers arise.

A 20 year old white man had had slowly developing curvature of the spine since he was 3 years of age. For the past one and a half years he had had difficulty in urination and in the past few weeks difficulty in walking. There was complete paraplegia in flexion of both lower extremities with anesthesia to pain and temperature up to the nipple line and disturbances of the bladder and rectum. There was leukocytosis (13,000), and there were albumin and pus cells in the urine. At necropsy the spinal cord was greatly enlarged, and the intermeningeal spaces were filled with a jelly-like xanthochromic substance. Throughout the middle and lower thoracic spinal segments was an intramedullary tumor. This tumor was cystic centrally, the cavity varying in size at the different levels. Where the tumor showed the least degenerative changes its true nature was easily made out. There it consisted of nests of ganglion and glial cells. In Bielschowsky preparations the ground substance was a meshwork of unmyelinated nerve fibers, many of which emanated from ganglion cells. The glial cells were rich in glial fibrils. In some areas the glial nuclei were arranged in parallel bands, giving the tumor a neurinoma-like appearance. Many of the ganglion cells were degenerated, and occasionally binucleated ones were seen. The degenerative changes in the central portion of the tumor which led to the formation of the cavity were easily followed. Both the gray and the white substance in the vicinity of the tumor showed degenerative changes. Of pathologic interest was that level of the spinal cord which showed superficial evidence, at least, of syringomyelia. We reserve the term "syringomyelia" for a definite clinical and pathologic entity the pathologic aspects of which have been described by Petrén and Hassin. All other cavities in the spinal cord, whether they are broken-down tumors as in our case or areas of softening, should be differentiated from true syringomyelia.

CARL W. APFELBACH, *President*

*Regular Monthly Meeting, Nov. 9, 1936*

EDWIN F. HIRSCH, *Secretary*

THE INADEQUACY OF ALLERGIC INFLAMMATION AS A PROTECTION AGAINST INFECTION OF RABBITS WITH VIRULENT PNEUMOCOCCI. PAUL R. CANNON and GEORGE HARTLEY JR.

The inflammatory reaction in bacterial infection is an important localizing mechanism. The localization is supposed to be due to a mechanical walling-off of the bacteria by the deposition of fibrin, the occlusion of lymphatics and the accumulation of phagocytic cells. According to this view, allergic inflammation, because of its greater intensity and speed of response, should insure more effective localization than normergic inflammation.

The outcome of the inflammatory response is variable, and a reaction effective against bacteria of low virulence or invasiveness may be ineffective against bacteria of high virulence. Such is the case in infection of rabbits with a virulent strain of type I pneumococcus. Small numbers of these micro-organisms (as few as from four to ten cocci) injected subcutaneously into normal rabbits cause a locally spreading lesion and death from septicemia within from thirty to forty hours. Similarly if the micro-organisms are suspended in 10 per cent crystalline egg albumin and injected subcutaneously into rabbits previously made hypersensitive to this protein, a locally spreading lesion and septicemia occur. Furthermore, allergic inflammation of from two to three hours' duration fails to prevent bacterial generalization when small numbers of pneumococci are injected directly into the field of inflammation. In sharp contrast to these findings, a subcutaneous injection of pneumococci into rabbits actively immunized against the same strain leads to sharply localized inflammation at the point of injection and survival of the animals.

It is evident, therefore, that the intensified and accelerated response during the early stages of allergic inflammation does not prevent dissemination of highly virulent pneumococci from the site of injection. Complete protection requires immunization, thus emphasizing the fundamental importance of immunity as compared with nonspecific inflammation even though intensified and accelerated as in allergic inflammation.

DISCUSSION

S. ROSENTHAL: Kahn observed that animals sensitized to horse serum are not protected against diphtheria toxin by small doses of horse antiserum. This failure shows a definite relation to allergy. The skin reaction of tuberculous animals disappears following injections of tuberculin. These animals are allergic in a different way. The use of sensitivity to egg albumin with pneumococcus antigen does not prove that allergy has no place in inflammation.

PAUL R. CANNON: The main point of my report is allergic inflammation, not allergy. With allergy the inflammation should be greater and develop faster. Kahn's experiments are an amplification of Opie's studies on the Arthus phenomenon. There is no question about the marked fixation of antigen in the Arthus reaction. The antiserum is bound so that large doses need to be given for protection. The fibrin barrier in highly susceptible animals does not prevent the spread of infection.

LOCALIZATION AND CONCENTRATION OF ANTIBODIES AND COLLOIDAL DYE IN AREAS OF INFLAMMATION OF VARIOUS AGES. JOHN P. FOX.

The experiments reported here were undertaken in an attempt to determine (1) whether antibodies from the blood stream may be localized in areas of inflam-

mation, and (2) what relationship exists between the age and stage of an inflammatory process and its ability to localize blood-borne materials.

Inflammatory lesions were created in rabbits' skin with three types of irritants: Bacillus typhosus vaccine, solution of calcium chloride (1:500) combined with a dilute solution of formaldehyde (0.4 per cent), and turpentine. After the lesions had been present for varying periods, large doses of test materials (trypan blue, hemolytic serum and agglutinating serum) were injected intravenously. With all three types of irritants, it was found that the youngest lesions concentrated the dye more rapidly and in far greater amounts than the older lesions. The power to localize blood-borne materials persisted for a longer time in the lesions produced with the stronger irritants. This was correlated with the persistence of a granulation tissue reaction about areas of local tissue necrosis. Where such necrosis did not occur, as in the cellulitis from injection of vaccine, the property of localization was lost after twenty-four hours, apparently because of some vascular interference. The latter type of reaction is somewhat comparable to such clinical types as lobar pneumonia and erysipelas, while the more severe processes, healing by granulation tissue, are like chronic processes, such as abscesses and other forms of encapsulated infections.

The localization of antibodies was less conclusively demonstrated, but in view of certain considerations indicated, was presumed to occur. As with the dye a correlation was observed to exist between the localization of antibodies and the age and severity of the inflammatory lesions. No evidence was found suggesting that antibodies might be more easily localized in inflammatory foci induced by the specific antigen.

The complete article will be published in the *Journal of Immunology*.

TRANSPOSITION OF THE ARTERIAL TRUNKS. MAURICE LEV and OTTO SAPHIR.

Six specimens of transposed arterial trunks are presented. Three show partial transposition, with the aorta and the pulmonary artery emerging from the right ventricle. In two of these there are hypoplasia and stenosis of the pulmonary ostium respectively. In the third there are hypoplasia of the aortic ostium and coarctation of the aorta. Specimens 5 and 6 show complete transposition, with the aorta emerging from the right ventricle and the pulmonary artery from the left ventricle (with a completely formed interventricular septum). The last specimen is one of truncus solitarius aorticus with pulmonary and tricuspid atresia.

The work of Pernkopf and Wirtinger (1933, 1935) on the embryology of the heart sheds much light on the problem of transposition. The movements of the heart during development may be divided into two phases. The first phase is concerned with the formation of the loop and the bayonet-like kink of the bulbus. During this phase torsion of 90 degrees occurs at the auriculoventricular and ventriculobulbar orifices in such a manner as to approximate medially the mesocardial portions of these regions. The second phase is concerned with the absorption of the bulbus and the shift of the auricular canal to the right. During this process torsion of 150 degrees occurs in a clockwise direction at the ostium bulbotruncare and back-torsion of 45 degrees at the ostium ventriculobulbare. The torsion at the distal ostium of the bulbus produces the normal winding about each other of the larger arterial trunks.

The prevailing theories of transposition are (1) abnormal rotation of the septum bulbi, (2) Spitzer's phylo-ontogenetic theory and (3) Keith's theory of the abnormal absorption of the bulbus. None of these theories is in complete accord with the anatomic facts of all types of transposition and with the ontogenetic findings of Pernkopf and Wirtinger. However, the fundamental assumption of Keith—that one is dealing with an abnormality in the absorption of the bulbus—is the most logical from the phylogenetic standpoint.

A theory of transposition is suggested, based on the hypothesis of Keith. Normally, during the second phase, the proximal end of the bulbus is rotated only 45 degrees owing to the close intimacy of the bulbus and the auricular canal at

the area of the bulbo-auricular spur. Thus the unwinding of the spiral of the bulbar ridges is achieved by torsion at the ostium bulbotruncare. In transposition, however, there is an abnormality in the area of the bulbo-auricular spur (a persistence of the primary bulbo-auricular spur) which prevents the formation of a fixed point in this area. This permits the greater back-rotation of the proximal ostium of the bulbus, and thus less torsion occurs at the ostium bulbotruncare, resulting in various degrees of transposition. When the back-torsion occurs about the junction of ridge A with the ventricular septum there is a restriction of the pulmonary ostium, while when it occurs about the center of the bulbus the two arterial ostia are of normal size, or the aortic ostium is restricted. Anatomic evidence as to the position of ridges A and B may be obtained by studying the position of the septal and parietal muscle bundles, the former being derived from ridge A and the latter partially from ridge B.

The various degrees of transposition may be classified in ascending order of back-torsion at the ostium ventriculobulbare as follows: riding aorta with an aneurysm of the membranous septum; riding aorta with a defect of the ventricular septum; aorta and pulmonary artery from the right ventricle; aorta from the right and pulmonary artery from the left ventricle (complete transposition); miscellaneous group—truncus communis, truncus solitarius aorticus, transposed trunks with atresia of the tricuspid valves.

Anatomic evidence from our series in favor of this theory is found in: the topography of the muscle bundles of the right side of the heart; the presence of abnormal muscle bundles passing through the defect of the ventricular septum, considered to be the bulbo-auricular spur; the atresia of the tricuspid valves in specimen 6; the pulmonary hypoplasia, stenosis and atresia in specimens 1, 3 and 6, respectively; the aortic hypoplasia in specimen 2.

DISCUSSION

Otto Saphir: In the consideration of the recognition of transposition of the arterial trunks it becomes evident that certain criteria aside from the relative position of the vessels themselves are of fundamental importance. These are the position of the coronary ostia, the coronary distribution and the topography of the muscle bundles of the right ventricle. The study of the muscle bundles previously undertaken by Spitzer, Pernkopf and Wirtinger and others yielded conflicting hypotheses as to their origin and topography. We therefore felt the necessity of restudying the normal and abnormal anatomy of the muscle bundles in a large series of cases. The results of this study, briefly alluded to, have yielded what we think is a key to the problem as to whether in a particular case the embryologic development of the bulbus has been normal or abnormal. And it is the abnormal absorption of the bulbus, as shown by the abnormality in the muscle bundles, which we think is the underlying abnormality in transposition.

Pleomorphic Cell Sarcoma of the Gallbladder. Alex B. Ragins.

Two pleomorphic cell sarcomas of the gallbladder are reported. Both gave rise to generalized metastases. The presence of gallstones or more particularly chronic inflammatory changes in the wall of the gallbladder may be considered a possible etiologic factor in these tumors.

# Obituaries

## WILLIAM BUCHANAN WHERRY

1875-1936

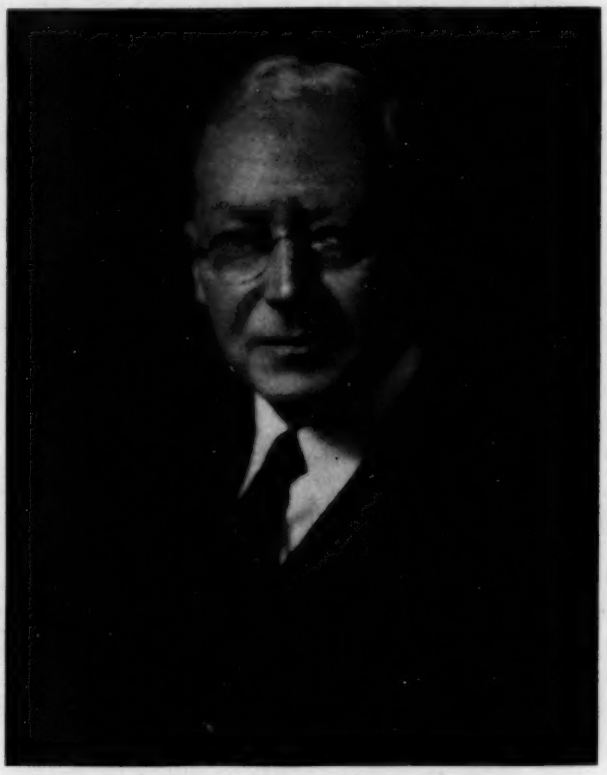
The hard work, self-discipline, selflessness and desire to have the truth prevail that characterize clergymen and scientists were infused into William Buchanan Wherry on Dec. 24, 1875, when born as one of seven children to Elwood Morris Wherry and his wife, Clara Maria Buchanan, both out of Western Pennsylvania but then active as Presbyterian missionaries in Ludhiana. A *Kim* out of India, he was to be more orthodoxly civilized when brought to Chicago at 14. Thereafter he attended Washington and Jefferson College to receive a bachelor's degree. The year 1897 saw him entered in Chicago's Rush Medical College.

More determinative than his scheduled schooling was his entrance into Ludvig Hektoen's laboratory. As a pupil of Chiari, Hektoen knew morphologic pathology to his finger-tips. The more remarkable, therefore, that he taught Wherry (and the rest) that this subject was dead. The new point of view, and progress, lay with bacteriology, with antigens and antibodies; and in those dynamic concepts of disease which regarded it as distorted physiology. Hektoen's effectiveness cannot be better demonstrated than by listing some of the men who at the moment of Wherry's entrance into the crowd fought for air in the five room first floor and basement (once a janitor's quarters) that constituted the research facilities of the pathologic laboratory of Rush Medical College —E. R. LeCount, George H. Weaver, H. G. Wells, E. C. Rosenow, T. R. Crowder, D. J. Davis, Peter Bassoe, Brown Pusey, Howard T. Ricketts, Arthur D. Dunn, Noble Wiley Jones, Rollin T. Woodyatt, Alice Hamilton and Martin H. Fischer.

Having learned thus early that only men are the producers of scientific discovery and scientific opinion, Wherry sought out Theobald Smith. And such a man-hunter he remained throughout life. The queue in Hektoen's laboratory being long, Wherry next became assistant to E. O. Jordan, not yet professor, but technically in charge of bacteriology in the University of Chicago. Two academic years of it (in which he was to meet his future wife, Marie Nast) and he was on his way to Manila. Via a competitive examination he had been appointed to the government laboratories. The rules of the competition declared the high man the pathologist, the next high the bacteriologist. Though

handicapped by a low mark for "experience," Wherry made top score. Typical of the man, that on the voyage over he should trade his own title for the secondary!

Wherry's earliest scientific thoughts came into print in the *Transactions of the Chicago Pathological Society*. Any attempt to catalog his later activities ends in three propositions: Most of his labors were devoted to (*a*) micro-organismal variation as related to the environ-



WILLIAM BUCHANAN WHERRY
1875-1936

ment, (*b*) the better growing of parasites without the host and (*c*) their better strangulation within it.

Wherry's first Manila papers dealt with the causes of various skin infections. In one, on contagious pemphigus, he reported the isolation of his Micrococcus pemphigi-contagiosi. Other papers dealt with cholera, glanders and plague. But they differed from similar discussions of the day by stressing the biology of the organisms concerned, relating their polymorphism to the titer of the medium or to its salt

content; the cholera red reaction to the availability of nitrites; the liquefying potentialities of glanders to the dryness of the gelatin, and so on. This hunt for variability was to reappear in many later contributions, thus to make Wherry an international authority in the field.

Wherry returned to the United States—much of the distance fourth class, which in Oriental waters means that the swine and the human beings receive common classification as "self-moving freight"—via British ports, stopping off to pay his respects to the men of Great Britain's Indian Medical Service. Some days at the Institut Pasteur proved less satisfying.

For a season, next, he was jobless in Chicago. Then, as expert to the Anaconda Copper Company, a fat salary revived him. But missing school and scientific associates, he accepted the professorship for parasitology in the newly born Oakland College of Medicine. Now married, he was happy, and in his new freedom wrote one of those (too few) general papers (on the biology of disease) that he could do so well.

Wherry's tropical reputation having preceded him into San Francisco, then in the tenth year of its agony over the plague, he was made its health board bacteriologist. Most of his time was spent in examination of the catch of the rat trappers. He reported shortly on 14,184 rats which had been subjected to autopsy; then on 30,000. In 1908 Wherry discovered, also, Stefansky's leprosy-like disease of rats on the Pacific Coast.

Wherry's activities in San Francisco made for frequent contact with the United States Public Health and Marine Hospital Service. Its personnel (J. D. Long, especially) remembered Wherry from Manila days and urged his appointment to an acting assistant-surgeonship, setting up a laboratory for him in an empty house in Oakland. Things would have progressed happily if in July of 1908 he had not received by special delivery a tin can from his friend William Stewart Taylor, practitioner in the Livermore valley, containing one dead ground squirrel. That night Wherry reported its anatomic lesions as typical of plague, its smears as carrying enormous numbers of bipolar staining rods. In the next days his cultures showed involutional forms and his inoculated rats began to die. Thus had Wherry discovered the existence of plague in the ground squirrels of California, established the endemic nature of the disease, explained the origin of the "sporadic" instances of human disease without the confines of San Francisco, and given new form to the principles of plague control, never thought of before.

Wherry communicated his findings to San Francisco, which at once sent an army into the field to shoot the ground squirrels. Unfortunately squirrels infested with plague stop running around to get themselves shot. Nevertheless out of some hundreds, one was discovered infected;

and all of three that had been picked up dead. These bacteriologic discoveries, too, were Wherry's, but working under the command of San Francisco, it was San Francisco which, on Sept. 11, 1908, made public a first report, claiming the honor as of Aug. 28, 1908. But the report did add that "practically the same findings have been obtained by acting assistant surgeon Wherry in the Oakland laboratory, and are reported under date of August 24." There was no mention of the Livermore experience.

Wherry's own exhibits came to print in December. Without the history here set forth and with the recitation merely of his laboratory findings, Wherry devoted most space to the men who before him had guessed that plague might exist in the West's ground squirrels. If these men were so sure, it is perhaps fair to ask why no action, based on this "knowledge," was ever written into the plague prevention measures of years that a veritable horde of health officers had set up!

Wherry's California experience yielded further papers—on rat leprosy, the infestation of flies with rat lepra bacilli, the appearance of streptococci in diplococcic form, the activity of Bacillus pestis-caviae as raticide, and the bacteriology of human plague derived from ground squirrels. There appeared, likewise, some straight-out zoologic studies of the exogenous parasites of California rodents.

But 1909 had sickened Wherry in his heart; so when Paul G. Woolley, just appointed to the chair of pathology in the newly created medical department of the University of Cincinnati, telegraphed him to come on for bacteriology, Wherry went. Here, for twenty-seven years Wherry functioned as the best loved of teachers and the largest producer of men for the new and the different in medicine. Successively assistant and associate professor, he was not made professor or head of an independent laboratory until Dean Christian R. Holmes did it in 1914. Operating on the lowest budget of any department, he was aided by the generosity of patients and friends. But having worried some one into an appreciation of his own needs, he would promptly assign the half of his winnings to some other department.

Scarce settled in Cincinnati, he waded into the existent forms of medical education. Out of his personal laboratory he described "the following protozoa, worm and mite" endoparasites of the California ground squirrels. In this paper appeared the following: "Ordinarily the mere recording of new species . . . is of little interest but since the rôle played by *O. Beecheyi* in the maintenance of plague on our Pacific Coast was definitely established (*vide* Wherry . . .)." Medical historians will note this unusual quotation of himself.

There followed a description of four Filaria loa, notes on twenty-two spontaneous tumors in wild rats, a quantitative study of the amebicidal

action of emetine and the experimental production (via the addition of various alcohols) of "spores" in a tubercle bacillus. The year 1913 brought the statement that the acid-fastness of this bacillus is also dependent on the nature of the medium—conditions favoring the synthesis of fats are required. At the same time he noted the transformation of an ameba into a flagellate through transference to distilled water and a higher oxygen level.

The year 1914 brought the announcement that Wherry had recognized in a meat cutter's inflammation of the eye an infection with Bacterium tularense, a discovery of G. W. McCoy and Charles W. Chapin in the year before, in the California ground squirrel. Again, just another "case," but *seen*—and so to the magnificent generalization! There had been a month of fruitless effort to cultivate the organism while keeping it alive, unseen, by passage through twenty-four guinea-pigs; then success by using the (modified) coagulated egg yolk medium of McCoy and Chapin and, to make it visible, new staining methods. Before the year closed he described a second case. Suspecting that the human infection had sprung from rabbits, Wherry asked the local board of health to send collectors into southern Indiana, where an epidemic had been on. Gunmen were again sent out but tularemic rabbits, too, stop running around to get themselves shot. From two specimens found dead, however, the organism was cultivated and the "danger of its transfer to man" made evident. Thus "rabbit fever" became a new clinical entity and established as a new menace to the human species.

In the summer of 1914, Wherry worked on phagocytosis, associating himself with the (soon to die) G. L. Kite, first to use the Barber pipet for cellular dissection. During 1916 and 1917 he continued his efforts at better cultural methods. Thus he found that the gonococcus thrived best at an oxygen pressure below the atmospheric, generalizing this discovery to "the majority of bacteria actively multiplying within the tissues of a host." Utilization of the fact enabled him successfully for the first time to cultivate Leptothrix innominata, of Miller. To his list of bacteria he now added some animal parasites and an explanation of the morphologic variations of diphtheria. In 1918 Wherry made the remarkable discovery that not the organisms or the toxins contained in pneumonic lung tissue are the origin of the toxic effects when lung tissue extract is injected into animals, but the lung itself. From this observation sprang the hunt for, and the isolation of, "tissue fibrinogen," subsequently to be made the subject of countless biochemic researches.

To the need of a proper tension of oxygen for optimal growth, Wherry next added the need of a proper concentration of carbon dioxide, bringing first proof of his contention in the instance of the

tubercle bacillus. Employing, then, his newly worked out cultural methods, he isolated a leptothrix from a case of Parinaud's conjunctivitis.

In his description of a leprosy-like disease in a parrot he recounted his first attempt to cultivate by these methods involving control of atmospheres the acid-fast bacilli discovered in the lung. After "six months" of it, he obtained no growth. Meanwhile he worked on spray-borne bacteria as the cause of respiratory infection, discovering, first, that bacteria get much more deeply into the lung than ordinarily believed, and, second, that after such infestation infection is not the usual but the unusual consequence. Thus he revived the entire question of what is ancillary to all infection.

In studying the bacterial parasites of human mucous membranes (1920) he isolated and described for the first time Bacterium melaninogenicum and Micrococcus minutissimus while making more precise our knowledge of Bacterium dûplex-nonliquefaciens and Micrococcus reniformis.

In 1925 Wherry turned advocate of the usefulness of dehydration methods and of dyes (gentian violet and acriflavine) in the combating of superficial infection. At the same time he published his first experiments on the detoxication of bacterial vaccines by other methods than those of heat, in the effort to maintain a higher antigenic value. Thus by the use of formaldehyde he secured a more active Shiga bacillus vaccine wherewith to immunize a larger fraction of his animals to doses of living bacilli that killed the controls. By this method, too, he reduced the toxicity of a typhoid vaccine which, employed therapeutically two years later, allowed him to show "the course of the disease shortened, the temperature" lowered and "the duration of the fever in treated cases" as of 27.5 days, against that of 39 days in the controls.

Wherry spent 1929 and 1930 as visiting professor to Manila's school of hygiene. While here he cultivated Hansen's bacillus out of human tissues, accomplishing this feat by harking back to his bacteriologic faith that for the growth of any parasite there is needed, besides a moist and nutritionally proper medium, the right pressures of oxygen and carbon dioxide. Wherry's success has been denied; to which it need merely be answered that many a painter has stood before a Raphael with identical pigments in his hands to prove himself incapable even of copying the master.

The work hours of Wherry's last three years were halved by illness. Myocarditis, followed by the peripheral manifestations of obliterative arterial disease, coronary sclerosis and anginal attacks, slowly undercut him. In spite of their daily threat to his life, he fought forward—visiting in his vacation months the Far East. Perhaps the happiest summer of his life was his last in Hawaii. There, against the background of a

thousand ill and those colleagues whom he loved, and surrounded by his family, his cardiac attacks came anew, to bring his life to a standstill in Cincinnati Nov. 1, 1936.

Landing from the train that had given him his last ride, his major baggage consisted again of a packing case filled with cultures which he had lugged by hand because he was distrustful of all porters. Years earlier he had arrived similarly in the United States with bottled snakes from India. From Manila he had come with major sections of the human body—plague infected; and from the mountains about Anaconda, with the glandered heads of several horses. Oakland had furnished him with a collection of stuffed rats. Hidden among his more definitely personal treasures were showers of insects, butterflies and moths. The latter, a too orderly sister burned one day.

He used his ebbing energies to add to his general disquisitions. One was the revision of his 1913 essays on the rôle of the medical man in the tropics; another stated his gospel of organismal and tissue hypersensitivity; a third, his methods and principles of desensitization. Those interested in the philosophy of the parasitic struggle as viewed by Wherry cannot do better than peruse these stimulating generalizations.

For the rest, he applied himself to: the direction of his co-workers, the establishment of a serum farm and the bringing forth of (by the use of his detoxicated antigens) antitularemic, antistreptococcic and antiundulant fever serums of many times the titer previously produced; also, more and better vaccines against the organisms associated with sinus infections, asthma and mucous colitis; painstaking work, too, on the bacteriology of the intestinal flora in pernicious anemia, the rheumatisms and arthritis. Under these headings "doctor" Wherry did much in the way of treatment—principally for "chronics" that a wearied medical profession had jettisoned.

Though his death brought him front page, life had presented him with no lengthy list of "honors." He was a member of but two national societies, and he died without medals or honorary degrees. Nevertheless, his hold on men was nothing short of startling. His soft-spokenness and his gentle smile were mistaken at times, but not by any who ever heard his dissenting voice in faculty or scientific debate. Children gravitated to him like the proverbial flies to honey; his laboratory animals became his pets, and the hopelessly ill clung to him even as he disparaged his own "science." Thus, without compromise, he carried to his graveside not only a personal but an official populace, proud indeed to have been of those nominated his "friends."

MARTIN H. FISCHER.

# Book Reviews

**Endocrinology in Modern Practice.** William Wolf, M.D., M.S., Ph.D. Cloth. Price $10. Pp. 1018, with 252 illustrations. Philadelphia: W. B. Saunders Company, 1936.

This book was written "to provide the practitioner with a full and usable knowledge of clinical endocrinology." The first and major part deals with the glands of internal secretion and certain other topics as shown by the following list of subjects of chapters: the subject of endocrinology, the pituitary gland, the ovaries, the testicles, the thyroid gland, the adrenal glands, the parathyroid glands, the thymus glands, the pancreatic islands, other hormones, obesity, menstrual disorders, the menopause, pregnancy and sterility. The chapters on the endocrine glands describe the anatomy, embryology, histology, physiology, biology and diseases of these glands. Special stress is laid on diagnosis and treatment. The second section is devoted to "endocrine aspects of each of the more commonly practiced specialties." This section includes chapters on surgical and orthopedic diseases, diseases of children, nervous and mental diseases, diseases of the gastro-intestinal tract, diseases of the cardiovascular system, diseases of the genito-urinary system, diseases of the skin, diseases of the eye, diseases of the ear, nose and throat, and diseases of the oral cavity. Then comes a section on diagnosis, with chapters on the taking of the history, physical examination, bone development and anthropometry, the interpretation of laboratory findings, and the choice and description of diagnostic procedures. Finally, endocrine preparations are discussed in two chapters, one on the character and dosage of commercially available endocrine products and one on the use of endocrine preparations for their pharmacologic action. There is a good and full subject index. At the end of each chapter of the first three sections are summaries for reference and review. According to the preface, the important contributions to the literature of endocrinology up to June 1936 were reviewed in the preparation for writing the book, but all bibliographic references have been omitted "because of the vastness of the available literature in endocrinology and on account of the general character of the book." There can hardly be any question but that a list of selected references at the end of each chapter would have added a good deal to the value of the book. The illustrations, all black and white, serve their purpose well. The style is fluent, with a trend to redundance. Occasionally there are lapses from desirable conservatism in statement, as illustrated by this paragraph on page 648: "Susceptibility to infections is often dependent upon a lowered functioning of the endocrine glands, causing physiologic depression and a lowering of the bodily resistance. The toxic condition therefore is closely related to asthenia, combined with and caused by inefficient action of the thyroid and adrenal glands. The administration of *thyroid extract*, with or without the addition of adrenal substance is a prudent measure, which offers support to the deficient glands and heightens the resistance in the early stages of *pulmonary tuberculosis, typhoid fever, infectious tonsillitis* and severe cases of the *exanthemata*" (italics in original). The clinician will find this a useful book. It contains a large amount of dependable information.

**British Masters of Medicine.** Edited by Sir D'Arcy Power, K.B.E., F.R.C.S., F.S.A., Consulting Surgeon and Archivist to St. Bartholomew's Hospital; Honorary Librarian, Royal College of Surgeons of England. Price, $3. Cloth. Pp. 242, with 33 illustrations. Baltimore: William Wood & Company, 1936.

In the editor's preface one reads: "The articles in this book are written by those who have been attached to the great institutions which their heroes made famous. They appeared originally in the pages of the *Medical Press and Circular*, as a series of articles under the title of 'British Masters of Medicine,' and were published during the years 1934 and 1935." This statement makes clear why a

tendency to hero worship pervades the pages. The writer, who in some instances was a student or junior colleague of the subject of the sketch, wishes to make out a good case for the hospital or school with which both were connected and which the master had helped to make famous. These articles, twenty-four in number, are trustworthy as to facts and in general as to the estimate placed on the man. In some instances the personality of the hero is emphasized at the expense of telling what he did and how he did that which made him worthy of remembrance. As is to be expected, where there are so many authors there is much variety in the manner of treating the topics and in the style of writing. Some articles seem rather dull; others are most attractively written. To the reviewer, the chapter on Harvey does not measure up to the greatness of the subject; that on Fergusson is not only informing but altogether excellent. Most of the "masters" are those whose names and works are familiar—Harvey, Sydenham, Hunter, Jenner, Paget, Lister, Mackenzie. Some are not so widely known, e. g., Floyer and Turner, yet are justly deemed worthy of remembrance, not so much because they wrote a great deal or made important discoveries as because they were superior practitioners, stimulating teachers, efficient executives or men whose personal influence and example left their mark on students and colleagues and tended to elevate the standard of medical practice and medical education. While not uninteresting to the student of medical history, the book will be of especial value to the undergraduate and the practitioner to whom many of these leaders in medicine are little more than names. It should arouse curiosity to know more of the lives and services of these truly great men.

**Histological Technic.** By Aram A. Krajian, Department of Pathology, Los Angeles County General Hospital, Los Angeles. Cloth. Pp. 217, with 5 illustrations. Los Angeles.

The author of this book has described in a clear, concise manner the fundamentals of the fixation, sectioning and staining of tissues. Thus it was possible to include in this book, in spite of its relatively small size, all of the staining methods used in the routine examination of normal and diseased tissues. The contents are divided into ten parts: tissue fixation and decalcification methods; equipment for sectioning, including microtomes and knives; technic of sectioning and mounting, with special consideration of frozen sections and their preservation; staining solutions, including all commonly used stains, such as the various hematoxylins, carmine, methylene blue, Gram, Giemsa, Van Gieson, etc.; clearing reagents; vital stains and routine nuclear stains; special or differential staining methods, such as stains for elastic fibers, fibrin, amyloid, hyalin, mucin, fat, bacteria, spirochetes, pigments and other special methods; histologic methods for the pathologic examination of the central nervous system, including stains for nerve tissue, glia, myelin sheath, etc.; miscellaneous methods, such as fixation of museum specimens, and an index. The author has made an excellent choice of methods, including modern as well as older ones, and they are clearly described. The reviewer misses only a few items, such as Maximow's hematoxylin-eosin-azure stain for the connective tissue cells. There are several minor oversights which could easily be amended in a second edition, such as an apparent contradiction in the method of preparing a 10 per cent solution of formaldehyde. However, the book will be a helpful and reliable guide for students, technicians and investigators.

**Medical Classics.** Compiled by Emerson Crosby Kelly, M.D., Department of Surgery, Albany Medical College. Price, $10 per volume. Pp. 78. Baltimore: The Williams & Wilkins Company, 1936.

*Medical Classics* is a periodical which will reprint in convenient and economical form original contributions of outstanding significance to medical literature. The papers selected will be reprinted without any abbreviation. Facsimiles of original pages may be used by way of illustration. In case the original paper was pub-

lished in a foreign language, the reprint will be accompanied by a "modern English translation." There will be concise, schematic biographies of the authors with reproductions of the best portraits available, complete bibliographies, and brief historical sketches of the subjects with which the reprinted papers are concerned.

The first number (September 1936) is devoted to Sir James Paget and his descriptions of osteitis deformans (Paget's disease of bone) and of disease of the mammary areola preceding cancer of the mammary gland (Paget's disease of the nipple). It is an attractive number—the paper, the format, the print, the reproductions are all appropriate and first class. The bibliography on Sir James Paget with index covers nineteen pages. *Medical Classics* has made a good start.

**The Harvey Lectures. Delivered Under the Auspices of the Harvey Society of New York, 1935-1936, Under the Patronage of the New York Academy of Medicine.** By Max Bergmann, M.D.; Robert M. Yerkes, M.D.; Peyton Rous, M.D.; B. A. Houssay, M.D.; John Farquhar Fulton, M.D.; Richard E. Shope, M.D.; Warren H. Lewis, M.D., and I. de Burgh Daly, M.D. Series XXXI. Cloth. Price, $4. Pp. 255, with illustrations. Baltimore: Williams & Wilkins Company, 1936.

This volume contains the following lectures: "Proteins and Proteolytic Enzymes" by Max Bergmann; "The Significance of Chimpanzee-Culture for Biological Research" by Robert M. Yerkes; "The Virus Tumors and the Tumor Problem" by Peyton Rous; "Relations Between the Parathyroids, the Hypophysis and the Pancreas" by B. A. Houssay; "The Interrelations of Cerebrum and Cerebellum in the Regulation of Somatic and Autonomic Functions" by John F. Fulton; "The Influenzas of Swine and Man" by R. E. Shope; "Malignant Cells" by Warren H. Lewis; "The Physiology of the Bronchial Vascular System" by I. de Burgh Daly. Each lecturer discusses mainly results or phases of his own work, and the lectures summarize well important advances in the fields of investigation represented.

**Text-Book of Pathology.** By Sir Robert Muir, M.A., M.D., Sc.D., L.L.D., F.R.S., Professor of Pathology, University of Glasgow; Pathologist to the Western Infirmary, Glasgow. Fourth Edition. Price, $10. Cloth. Pp. 994, with 571 illustrations. Baltimore: William Wood & Company, 1936.

This book is a new edition of a useful textbook of pathology for medical students, first published in 1924. The present edition incorporates without much enlargement of the book the advances since the third edition three years ago. Planned primarily for the medical student, the book deals with general pathologic processes and with structural changes in diseases in their bearing on clinical medicine. It is well written and unpretentiously but helpfully illustrated. Every page reflects years of experience as a teacher and of observation as a hospital pathologist by a master of pathology.

# Books Received

ARTIFICIAL PNEUMOTHORAX: EXPERIENCE OF THE LONDON COUNTY COUNCIL. F. J. Bentley. Medical Research Council, Special Report Series, no. 215. Paper. Price, 1 shilling, sixpence. Pp. 94. London: His Majesty's Stationery Office, 1936.

CERTAIN BIOLOGICAL PROBLEMS RELATING TO CANCER HORMONES, AND RADIATION. FIVE LECTURES. Delivered in the United States of America while the guest of the Anna Fuller Fund of New Haven and the International Cancer Research Foundation of Philadelphia, 1936. Antoine Lacassagne, assistant director, the Pasteur Laboratory Institute of Radium, Paris. Pp. 78.

HISTOLOGICAL TECHNIC. A Practical Handbook for the Workers in Histology or Histopathology Laboratories, Which Describes in Compact Form, Improved Methods for the Preparation of Microscopical Sections. Aram A. Krajian, Department of Pathology, Los Angeles County General Hospital. Cloth. Price, $3.50. Pp. 219, with 4 illustrations. Los Angeles: The Author, 1936.

THE RELATIONSHIP OF THE IODINE CONTENTS OF WATER, MILK AND PASTURE TO THE OCCURRENCE OF ENDEMIC GOITRE IN TWO DISTRICTS OF ENGLAND. By the Committee on Iodine Deficiency and Thyroid Disease, with Sections by Matthew Young, and M. G. Crabtree and E. M. Mason. Medical Research Council, Special Report Series, no. 217. Paper. Price, sixpence. Pp. 20. London: His Majesty's Stationery Office, 1936.

TEXT-BOOK OF PATHOLOGY. Sir Robert Muir, M.A., M.D., Sc.D., L.L.D., F.R.S., professor of pathology, University of Glasgow; pathologist to the Western Infirmary, Glasgow. Fourth edition. Cloth. Price, $10. Pp. 994, with 571 illustrations. Baltimore: William Wood & Company, 1936.

BRITISH MASTERS OF MEDICINE. Edited by Sir D'Arcy Power, K.B.E., F.R.C.S., F.S.A., consulting surgeon and archivist to St. Bartholomew's Hospital; honorary librarian Royal College of Surgeons of England. Cloth. Price, $3. Pp. 242, with 33 illustrations. Baltimore: William Wood & Company, 1936.

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